Asymmetric Reduction of Functionalized Ketones and Their Synthetic Applications

by

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Contents

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I appreciate the help and encouragement from my friends, you know who you are and you are the blessing in my life.

Finally, I'm able to complete this mission because of my parents; their dedication I will never forget.

Declaration:

The research described in this thesis is solely the work of the author unless otherwise stated. The studies were carried out at the Department of Chemistry, University of Warwick between October 2010 and August 2013. The content of this thesis has not been submitted, either wholly or partially for a degree at any other academic institution.

Some of this work has appeared in the scientific literature in the following publications:

1. Dissociation and Hierarchical Assembly of Chiral Esters on Metallic Surfaces. B. Moreton, Z. Fang, M. Wills, G. Costantini, *Chem. Commun.*, **2013,** *49,* 6477-6479.

2. Asymmetric Transfer Hydrogenation of Functionalised Acetylenic Ketones. Z. Fang, M. Wills, *J. Org. Chem.*, **2013,** *78,* 8594-8605.

3. Asymmetric Reduction of 2,2-Dimethyl-6-(2-oxoalkyl/oxoaryl)-1,3-dioxin-4-ones and Application to Total Synthesis of Yashabushitriol. Z. Fang, G. J. Clarkson, M. Wills, *Tetrahedron Lett.*, **2013,** *54,* 6834-6837.

Abstract:

Asymmetric transfer hydrogenation (ATH) represents a powerful methodology for the synthesis of chiral secondary alcohols. The synthesis of chiral propargylic alcohols by asymmetric transfer hydrogenation of acetylenic ketones has been applied to a number of applications including target oriented synthesis.

In this thesis, the asymmetric transfer hydrogenation of a large number of functionalized alkyones and dialkyones has been fully investigated. Basic principles as well as detailed reaction conditions for the ATH of acetylenic ketones have been established. Chiral propargylic alcohols have been successfully prepared by a new method that was developed during this project and some of the products and strategies were used for the total synthesis of (-)-yashabushidiol B and panaxjapyne A.

Moreover a group of aromatic ketones functionalized with the 1,3-dioxin-4-one scaffold were prepared and used as substrates for asymmetric transfer hydrogenation. Detailed reaction conditions such as catalyst loading, temperature, substitution effects and stability of substrates were fully investigated. Reduced products were prepared in a highly stereoselective manner and the utility of this method and the resulting chiral alcohols have been illustrated by the total synthesis of yashabushitriol.

The application of ATH to the preparation of a highly optically pure ester for scanning tunnelling microscopy (SCM) dissociation and hierarchical assembly was also undertaken.

Abbreviations:

^{o}C:	Degrees Celsius
δ_C:	^{13}C-NMR chemical shift (ppm)
δ_H:	^{1}H-NMR chemical shift (ppm)
$[\alpha]_D$:	Optical rotation
Ac:	Acetyl
Ar:	Aryl
ATH:	Asymmetric transfer hydrogenation
BINAP:	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL:	1,1’-Bi-2-naphthol
Bn:	Benzyl
Bt:	*N*-Benzotriazolyl
n-Bu:	*n*-Butyl
Cod:	1,5-Cyclooctadiene
Conv.:	Conversion
Cp*:	Pentamethylcyclopentadien
Cs:	Cyclohexlysulfonyl
CYDN:	1,2-Cyclohexanediamine
d:	Doublet
DABCO:	1,4-Diazabicyclo[2.2.2]octane
DACH:	1,2-Diamino-cyclohexane
DCM:	Dichloromethane
DKR:	Dynamic kinetic resolution
DMF:	*N*,*N*-Dimethylformamide
DMP:	2,2- Dimethoxylpropane

DMSO:	Dimethylsulfoxide
DPEN:	1,2-Diphenylethlyene-1,2-diamine
ee:	Enantiomeric excess
EI:	Electron impact
ESI:	Electrospray ionisation
Et:	Ethyl
Equiv:	Equivalent
FA:	Formic acid
FID:	Flame ionisation detector
GC:	Gas chromatography
HPLC:	High performance liquid chromatography
h:	Hours
HRMS:	High resolution mass spectrometry
IPA:	Isopropanol
LDA:	Lithium diisopropylamide
Lit.:	Literature
m:	Multiplet
M:	Mol/dm^{-3}
m-CPBA:	*meta*-Chloroperoxybenzoic acid
Me:	Methyl
min:	Minutes
MP:	Melting point
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid
m/z:	Mass to charge ratio
NMR:	Nuclear magnetic resonance

o-:	*Ortho*
p-:	*Para*
PCC:	Pyridinium chlorochromate
Ph:	Phenyl
PODPEN:	1-Diphenylphosphinic-1,2-diphenylethlyene-1,2-diamine
ppm:	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr:	Isopropyl
Py:	Pyridine
q:	Quartet
rt:	Room temperature
s:	Singlet
t:	Triplet
TBDPS:	*tert*-Butyldiphenylsilyl
TEA:	Triethylamine
Temp.:	Temperature
TFA:	Trifluoroacetic acid
THF:	Tetrahydrofuran
Tof:	Turnover frequency
Ts:	*para*-Toluenesulfonyl/ Transition state
TsDPEN:	*N*-Tosyl-1,2-diphenyl-1,2-diaminoethane
TsEN:	1,2-Diphenyl-1,2-diaminoethane
υ_{max}/cm^{-1}:	Wave number (cm^{-1})

1. Introduction:

1.1. Asymmetric Synthesis

Asymmetric synthesis is a process that directly produces an optically active compound from symmetrically constituted molecules without requiring resolution of a racemic mixture. It involves the creation of a new stereocentre by stereoselective reactions on a starting molecule that may be symmetric or asymmetric. Asymmetric synthesis can broadly be divided into three types depending on the strategies used. 1. Asymmetric induction through diastereoisomer formation. 2. Asymmetric catalysis. 3. Chiral pool synthesis.

1.1.1. Asymmetric Induction through Diastereoisomer Formation.

Asymmetric induction can be achieved by the preferential formation of one diastereoisomer over the other as a result of the influence of a chiral feature present in the substrate, reagent or environment. It can be further divided into internal asymmetric induction and external asymmetric induction (chiral auxiliary approach).

1.1.1.1. Internal Asymmetric Induction.

The presence of a stereocentre in a substrate can influence the formation of a new chiral centre in order to form a more complex enantiomerically enriched product. The effects of internal asymmetric induction have been studied extensively and a number of rules and models have been discovered. To understand how the stereogenic centre controls the formation of the new stereogenic centre during the course of a reaction, several models and transition states have been proposed. For example, Cram's[1] rule was proposed by Cram in 1952 and has been widely used to explain how the adjacent stereocentre affects the addition direction of nucleophilic reagents by steric hindrance. For example (**Figure 1**)

if using a Grignard reagent to attack aldehyde **1** which bears a chiral centre at the α position the products are unlikely to be generated in 1/1 ratio; instead the direction of the Grignard reagent addition is influenced by the chirality of compound **1** which results in unequal formation of products **2** and **3**. The major conformation is assumed to be that in which the C=O group is *trans* to the large group on the adjacent C atom. The nucleophile approaches from the face obstructed by the smaller group.

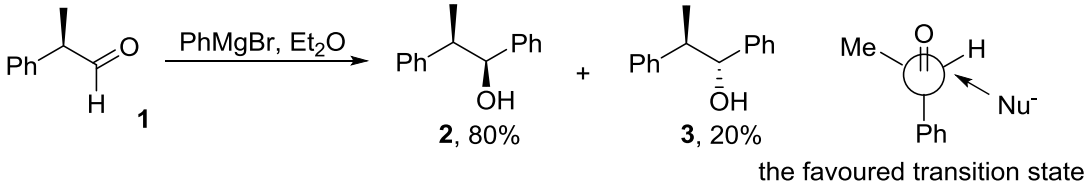


Figure 1. Example and favoured transition state of Cram's rule.

Subsequent Felkin model[2] and Felkin-Anh model[3] further extended the substrate scope and added orbital factors into the asymmetric induction system. Other rules such as the Cram-chelation model,[4] chelation model[5] and non-chelation model[6] for 1,3-induction have also been proposed to explain the different stereoselective experimental results.

1.1.1.2. External Asymmetric Induction-The Use of Chiral Auxiliaries.

In order to control the stereochemistry, an external chiral source (chiral auxiliary) can be incorporated temporarily into the substrate and this can be removed and recycled after reaction is complete. One well known and most widely used chiral auxiliary is the Evans oxazolidinone auxiliary **4**. The Evans auxiliary[7]can be coupled with an acid chloride to form a chiral N-acyloxazolidinone **5** which induces *syn* diastereoselectivity via Bu_2BOTf or tetrachlorotitanium promoted aldol reactions and also controls the absolute configuration of the aldol product **6** at the same time (**Figure 2**).

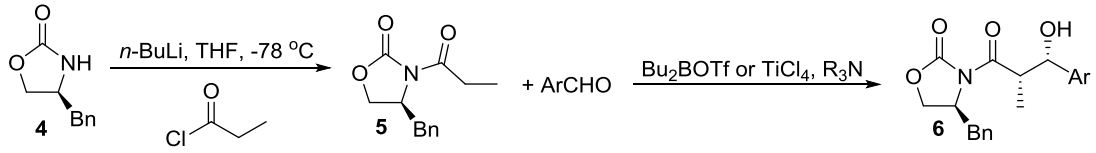


Figure 2. Example of Evans auxiliary facilitated aldol reaction

Other chiral auxiliaries such as (*S,S*)-psuedoephedrine[8] and *tert*-butanesulfinamide[9] have received considerable attention since they were originally developed.

Chiral auxiliary approaches, because of their generally reliability and versatility have been widely utilized in synthesis of enantiomerically pure compounds and natural products.

1.1.2. Asymmetric Catalysis.

Asymmetric catalysis, in which each molecule of catalyst, by virtue of being continually regenerated, can yield many molecules of chiral product, has significant potential advantages over other means.[10] Several processes involving asymmetric catalysis have been commercialized due to their molecular efficiency. Asymmetric catalysis has long been accepted by scientists for laboratory scale synthesis and its impact in the field of organic chemistry is growing. Extensive amounts of work involving asymmetric catalysts and asymmetric catalysts promoted reactions have been published, and how the enantioselective catalysts work, i.e. detailed mechanistic studies, has been widely investigated.

Asymmetric catalysis, due to the chiral environment created during transformation, operates by decreasing the transition state energy of one configuration relative to the other. This imbalance between the energy of the two transition states causes the enantiomer derived from the lower transition state energy to be synthesised more rapidly than the other.[11]

1.1.2.1 Transition Metal Based Asymmetric Catalysts.

To date, transition metal promoted asymmetric catalysis has made a wide selection of organic reactions possible.[12] Transition metal catalysis has been broadly developed and has become increasingly important in laboratory scale synthesis as well as industrial production.

A broad range of ligand types as well as catalyst complexes have been developed; whilst it is not possible to classify the types of catalysts in detail within this introduction, by function they include hydrogenation/transfer hydrogenation,[13] cross coupling,[14] metathesis,[15] oxidation[16] and many other applications of different types.

1.1.2.2 Asymmetric Organocatalysis.

Asymmetric organocatalysis[17] refers to asymmetric reactions that can be catalysed by organocatalysts. Organocatalysis was recognized as an environmentally-friendly alternative to transition-metal based catalysts especially in the pharmaceutical industry as toxic metals are eliminated from products. Organocatalysts can be inexpensive to prepare, stable and the reactions could be performed under aerobic environment. It is also recognized as a bridge between metal catalysis and enzyme catalysis. More interestingly, activation pattern of organocatalysts are different from metal catalysis. The scope of asymmetric reactions has been extended tremendously thanks to the development of new activation methods.

An example at the beginning of 21st century, a proline-(**8**)-catalyzed direct asymmetric aldol reaction[18] was first published by the Barbas III group (**Figure 3**). This example perfectly demonstrates how simple the organocatalyst and the reaction can be.

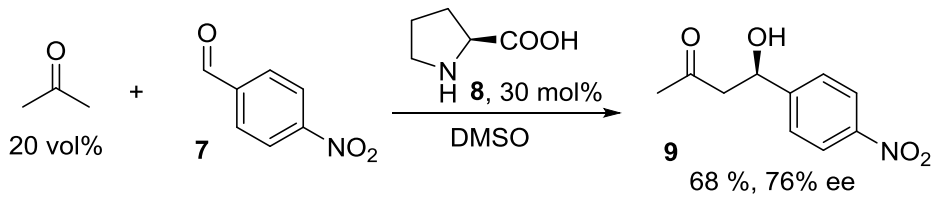


Figure 3. L-Proline catalyzed asymmetric aldol reaction.

1.1.2.3 Enzyme Catalysis.

Enzymes are biological macromolecules that can be used as biocatalysts for stereoselective chemical reactions.[19] Enzyme catalysis is characterized by high catalytic activities and selectivities, achieved under mild conditions. However, compared to synthetic catalysts, the catalytic pool of enzymes is limited. There are many features of enzyme catalysis: firstly, enzymes show high specificities toward their physiological substrates; compounds that differ only slightly from the natural substrate are often not acted upon. Secondly, the activity of many enzymes can be tuned, allowing the metabolism to proceed at a rate optimal for the well-being of the organism. Thirdly, enzymes can bring about enormous rate accelerations.

Enzyme catalysed reactions have been investigated and applied to natural product biosynthesis. Even small chiral molecules can be obtained by enzyme catalysis as an alternative to traditional organic reactions. For example, one of the most widely studied enzymes in organic chemistry is carbonyl reductase[20] which can reduce ketones to the corresponding alcohols stereoselectively (**Figure 4**).

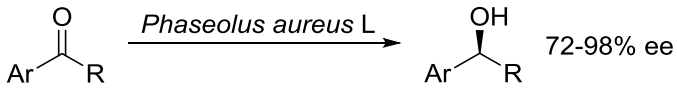


Figure 4. Asymmetric ketone reduction by carbonyl reductase.

1.1.3. Chiral Pool Synthesis.

Enantiomerically enriched compounds may be obtained by chemical transformations from enantiomerically enriched precursors, often derived from Nature's chiral pool. Chiral compounds derived from nature such as tartaric acid, D-mannitol and ascorbic acid have been applied abundantly in the total synthesis of natural products. An example of the synthesis of the natural product (*S*)-minquartynoic acid **12** in enantio-pure manner from L-(+)-tartaric acid **10** is illustrated in **Figure 5**.[21]

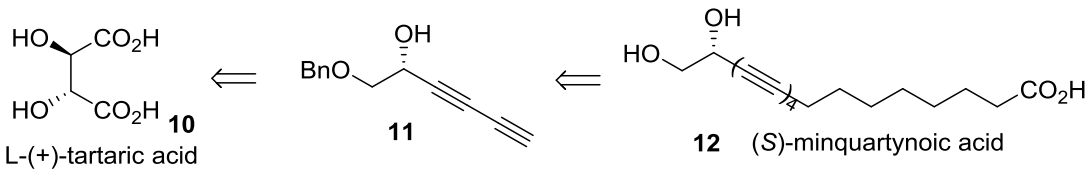


Figure 5. Asymmetric synthesis from natural chiral pool.

1.2 Transition Metal Catalysed Asymmetric Transfer Hydrogenation of Ketones.

1.2.1. A Short History of Asymmetric Transfer Hydrogenation.

The asymmetric transfer hydrogenation (ATH) of ketones is one of the most convenient and extensively studied transformations in organic chemistry. The benefits, including excellent selectivity, operationally simplicity and wide substrate scopes, have led to their broad applications to the synthesis of secondary chiral alcohols and related natural products.

To date, several categories of substrate, including aromatic/aliphatic ketones, imines and compounds with activated C=C bonds such as α,β-unsaturated ketones, cyanoolefins and dicyanoolefins have all been found to be active substrates for ATH reactions.[22]

Different types of catalyst complexes have been prepared and screened (**Figure 6**). At first, chiral diphosphine ligands, and bipyridine based ligands, were developed and applied to

transfer hydrogenation in 2-propanol at elevated temperatures. However, only poor enantioselectivities and reactivities were found.

When complex **15**-[$HRu(CO)_2$] was used the reaction had to be carried out at 120 °C; after 111 h the resulting (*S*)-1-phenylethanol (*S*)-**14** was obtained with only 35% yield and 4% ee.[23] When **16**-[$RuBr_2$] complex was applied the same product chiral 1-phenylethanol **14** was formed in 80% yield and 52% ee.[24]

No success was achieved when a bipyridine based ligand **17** was used in ATH of acetophenone **13**.[25] Instead of bipyridine ligand, improvement was achieved by using a chiral bioxazole ligand. Plaftz reported by using **18**-[$Ir(cod)Cl_2$] complex, in which case the enantioselectivity of formation of chiral 1-phenylethanol reached 58% ee and it was isolated in good yield (89%).[26]

Diphosphine-diamine **19** and diphosphine-diimine **20** ligands were combined with the same metal core; [$Ru(DMSO)Cl_2$], to form catalytic complexes by the Noyori group. Interestingly, when the two complexes were tested under the same reaction conditions the results were totally different. The enantioselectivity and reactivity of the diphosphine-diamine-[$Ru(DMSO)Cl_2$] (**19**-[$Ru(DMSO)Cl_2$]) complex was remarkable. The reduction of acetophenone **13** proceeded from room temperature to 45 °C with only 0.5 mol% of [$Ru(DMSO)Cl_2$] and both excellent yield (80%) and ee (52%) were achieved. When a **20**-[$Ru(DMSO)Cl_2$] catalyst was tested there was almost no conversion and also the ee was poor (18%). The authors claimed that catalyst **20**-[$Ru(DMSO)Cl_2$] is less effective because of the lack of NH functionality.[22c, 27]

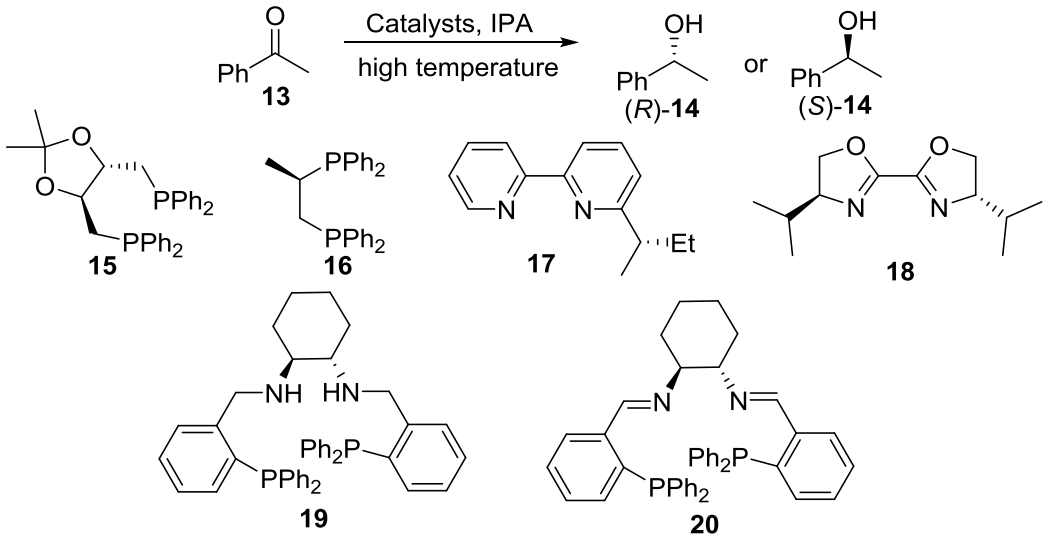


Figure 6. ATH with different ligands.

1.2.2. Ligands with NH Functionality.

Ligands that incorporate NH functionality have attracted significant attention. In 1995, Noyori's group reported a ruthenium catalyst [$RuCl_2$(mesitylene)]-(*S*,*S*)-TsDPEN **21** for asymmetric transfer hydrogenation of prochiral aromatic ketones at low catalyst loadings (S/C=200-500). This reduction could be carried out at room temperature in 2-propanol in a very efficient manner. Excellent ee values (up to 98%) and yields (up to 98%) were obtained by this catalyst. The authors also elaborated the reason why they used $[RuCl_2(arene)]_2$ to form the catalyst complex. The special function of the arene which is coordinated with Ru are as follows: (1) arene ligands automatically occupy three adjacent coordination sites of Ru in an octahedral coordination environment, leaving three sites with a *fac* relationship for other functions; (2) arene ligands are relatively weak electron donors which may provide a unique reactivity on the metallic centre; (3) ready modification of the substitutions of the arene is possible.

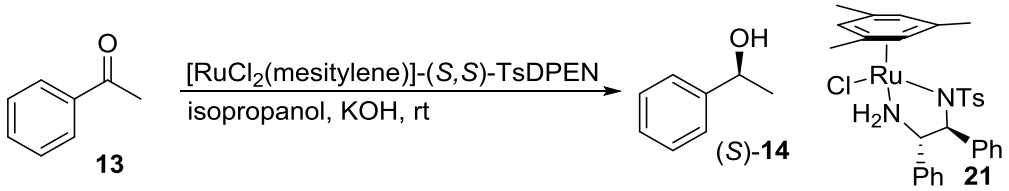


Figure 7. ATH by TsDPEN ligand.

After extensive investigation the conclusions were: (1) high enantioselectivity was obtained only when an appropriate arene and chiral ligand were combined; (2) the presence of a primary or secondary amine end in the amino alcohols/diamine ligands is crucial for the catalytic activity.[28, 22c]

In addition to TsDPEN **22**, other amine ligands such as TsDACH **23** and β-amino alcohols **24-26** (**Figure 8**) have been combined with $[RuCl_2(arene)]_2$ (usually the arenes are benzene, p-cymene, mesitylene and hexamethylbenzene) and excellent results were achieved in the transfer hydrogenation of aromatic ketones.[29]

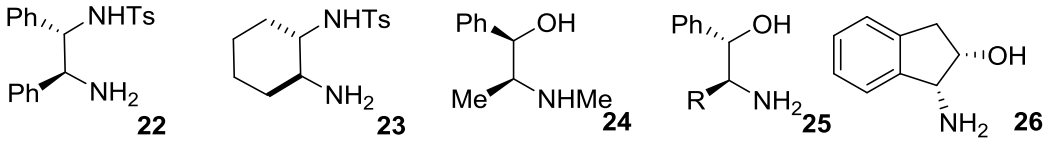


Figure 8. Different structures of ligands with NH functionality.

1.2.3. Tethered Catalysts.

The tether that links the mono-tosylated diamine ligand to the arene ring was first introduced by Wills's group. Due to the linking through the tether this catalyst exhibits higher catalytic activity compared to the original untethered catalysts. The authors believe that the tether serves to prevent the rotation of the arene ring, thus offering the potential for the addition of functional groups at various positions in a predictable manner. Another benefit of the tether is it can enhance the stability of the catalyst.

Taking the ATH of acetophenone **13** as an example (**Figure 9**), the tethered catalyst (*R*,*R*)-**c2** was capable of reducing of 200 molecules of **13** at 28 °C within 3 h (96% ee). The

(*R*,*R*)-**c2** catalyst could also be used at elevated temperature; at 40 °C (*R*,*R*)-**c2** could efficiently complete the conversion of 1000 equivalents of acetophenone within 5 h and the substrate loading could even reach up to 10,000/1. The enantioselectivity of **14** remains at the same level as the Noyori catalyst but it is more applicable to ketones which are not so active under previous reported conditions, for example hindered ketones.[30]

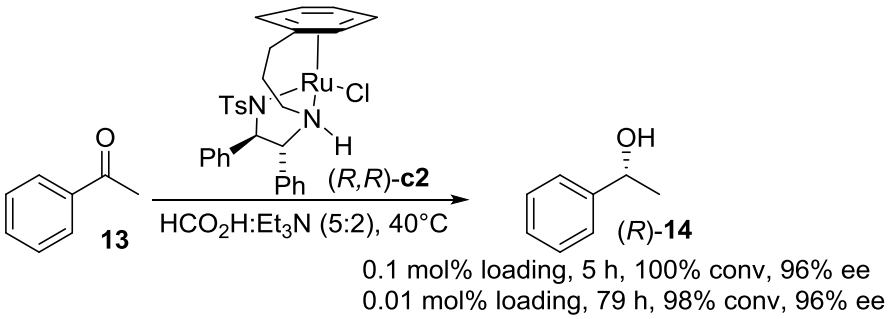


Figure 9. ATH of **13** by tethered catalyst (*R*,*R*)-**c2**.

Following this initial report, catalysts containing different tethers were prepared by Wills et al. (**Figure 10**), including tethers that incorporate an aromatic group **27**-**29**,[31] dimethyl **30**[32] and even a heteroatom such as oxygen **31**. Several of these catalysts share the same reactivity whilst the tethered catalyst with an amino alcohol ligand proved to be less active and less stable.

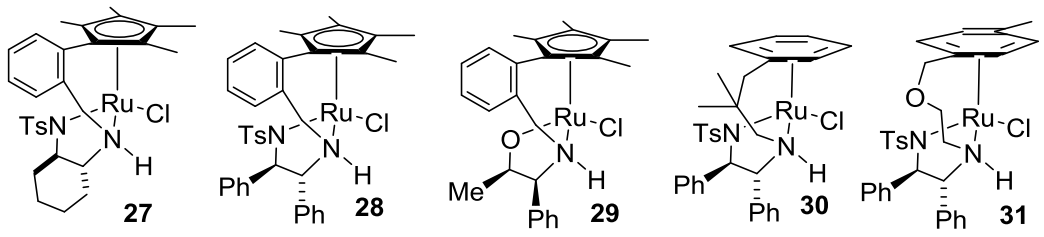


Figure 10. Structures of tethered catalysts.

The Ikariya group reported the oxo-tethered catalyst **31** before the report on the same complex by Wills et al. Asymmetric transfer hydrogenation of acetophenone **13** using the oxo-tethered complex **31** in HCO_2H/TEA 5/2 mixture proceeded rapidly; 1000 molecules of **13** can be fully reduced per catalyst molecule in 3 h at 60 °C (97% ee). From the experimental results catalyst **31** is more active than the four-carbon tethered catalyst **32**

(**Figure 11**). Catalyst **31** could also be used for asymmetric hydrogenation of ketones. Hydrogenation of aromatic ketones at 60 °C in methanol afforded the corresponding products with excellent ee values (**Figure 12**).[34]

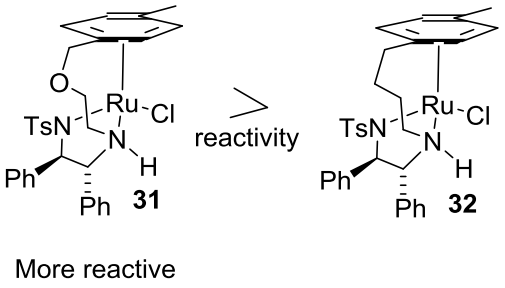


Figure 11. Catalytic reactivity difference between catalysts **31** and **32**.

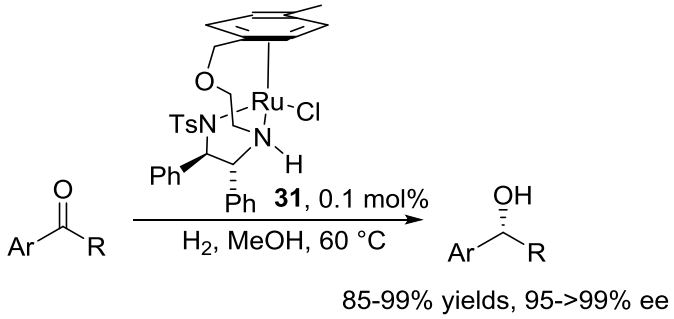


Figure 12. ATH of aromatic ketones of catalyst **31**.

The tether can also be linked at the sulfonamide side for example the mono-sulfonylated diamine tethered catalysts[35] **33-35** and the *N*-methyl-sulfamoyl-tethered catalysts[36] **36** and **37** which have also been reported. These catalysts could reduce acetophenone **13** efficiently but compared to other tethered catalysts their enantioselectivities were relatively low. From Wills's report, using arene modified catalysts for acetophenone **13** reduction the ee values only reached up to 68% (**Figure 14**).

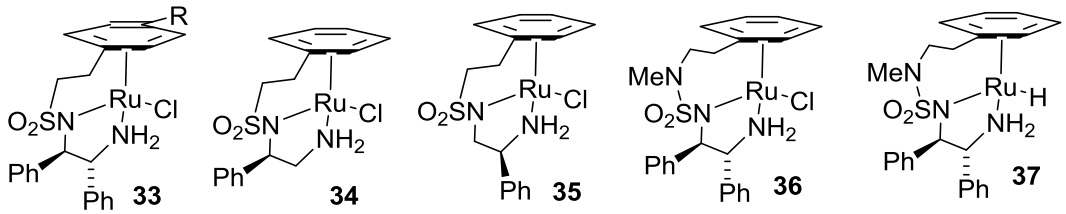


Figure 13. Catalysts that tether at the sulfonamide side.

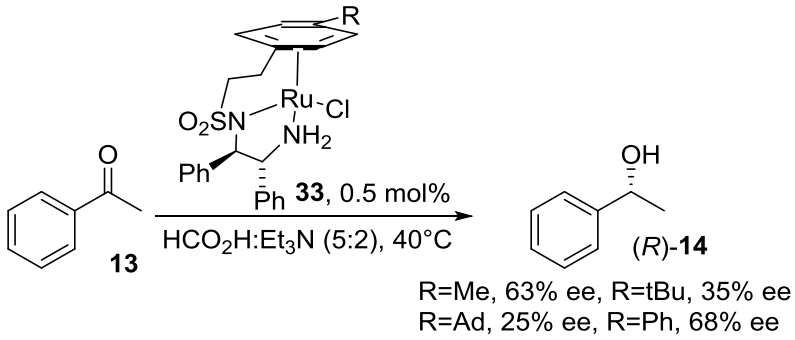


Figure 14. ATH by tethered catalysts.

One advantage of a tethered catalyst was discovered by Mohar et al.[37] From previous reports, for some reason the asymmetric transfer hydrogenation of 1-naphthyl ketones always proceeded with low enantioselectivities. With regards to the ATH of 1-acetonaphthone, catalyst **21** could only provide a product of 83% ee in HCO_2H/TEA 5/2 mixture but 93% ee in isopropanol, whereas both tethered TsDACH catalyst **27** and O-linked catalyst **31** could provide 84% ee in HCO_2H/TEA 5/2 mixture.[31, 33] Catalyst **37** demonstrated exceptionally high enantioselectivities in the ATH of 1-naphthyl ketones (**Figure 15**); products with up to 99.9% ee values could be prepared without any further processing/purification.

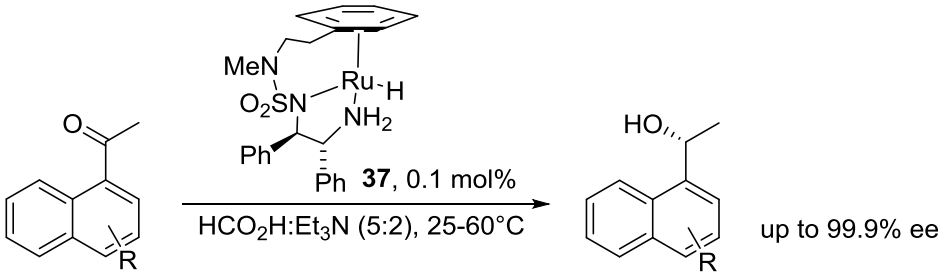


Figure 15. Advantageous effect of catalyst **37** in reduction of 1-naphthyl ketones.

1.2.4. Mechanism of ATH of Bifunctional Ruthenium Catalysts.

In the mechanism of asymmetric transfer hydrogenation, it has been proposed that a hydride from the ruthenium and a proton from the amine of the 18e ruthenium hydride amine intermediate are delivered to ketone through a rate-determining six-membered

pericyclic transition state (**Figure 16**). This has been supported by quantum chemical calculations.[38]

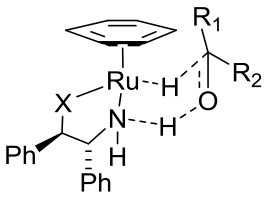


Figure 16. Pericyclic transition state of hydrogen transfer.

The six-membered pericyclic transition state was experimentally supported by the kinetic isotope effect measurements as reported in both Noyori and Casey's publications.[39] In reality, a sufficiently fast non-concerted reaction that is rapid compared to the applied detection method may be occasionally taken as a concerted reaction. In addition, a significant acceleration of reaction rates in the ATH of acetophenone with Ru[TsDPEN](η^6-*p*-cymene) **c1** catalyst in a binary water/co-solvent mixture has been discovered. The authors claim that reaction rates were observed to increase with the increasing polarity of co-solvent in a manner that is not characteristic of pericyclic reactions.[40]

Meijer also reported that the interaction of acetophenone with the hydrido complex RuH[N-(*p*-X-phenyl)-*N'*-(*p*-toluenesulfonyl)-1,2-ethylenediamine](η^6-*p*-cymene) in HCO_2H/NEt_3 mixture via a pericyclic transition state is not plausible, and that CO_2 interacts with the same complex (reverse reaction) possibly via an ion-pair intermediate.

Evidence from computational calculations which involve solvents suggest: (1) the activation barriers are lowered and the concerted mechanism predicted in the gas phase is converted into a sequential mechanism in methanol solution with the substrate appearing as a methoxide-like intermediate, which exists for a short but finite time in the reactive trajectory. (2) a concerted transition state was observed in aqueous solution, however, only

the hydride was transferred at that point, whereas the proton was transferred later by a water molecule.[41]

In 2012, the Ikariya group published a mechanistic study of asymmetric transfer hydrogenation of ketones catalyzed by the bifunctional ruthenium complex (*S*)-[RuH[(*R*,*R*)-OCH(Ph)CH(Ph)NH_2](η^6-benzene)] and (*S*)-[RuH[(*R*,*R*)-p-TsNCH(Ph)CH (Ph)NH_2](η^6-mesitylene)].

The reaction of [(*S*)-RuH[(*R*,*R*)-OCH(Ph)CH(Ph)NH_2](η^6-benzene)] with acetone was studied in the gas phase as well as in the continuum solvent reaction field of isopropanol using the SMD solvation model. The gas phase modelling is in agreement with previously reported data. The optimized concerted transition state (**$Ts_{1\text{-}2}$** in **Figure 17**) ΔE is 15.1 kcal/mol which is much higher than the highest energy transition state (**Ts_2** in **Figure 18**) of ΔE=11.5 kcal/mol calculated in continuum solvent reaction field. The major barrier to the hydride transfer (**Ts_1** in **Figure 18**) in solvent is ΔE=9.8 kcal/mol which suggests that hydride transfer can only break the Ru-H and form the new C-H bond at this point. The calculated barrier for the proton transfer (**Ts_2** in **Figure 18**) is ~2 kcal/mol higher than the barrier of the hydride transfer on both electronic and free energy scales.

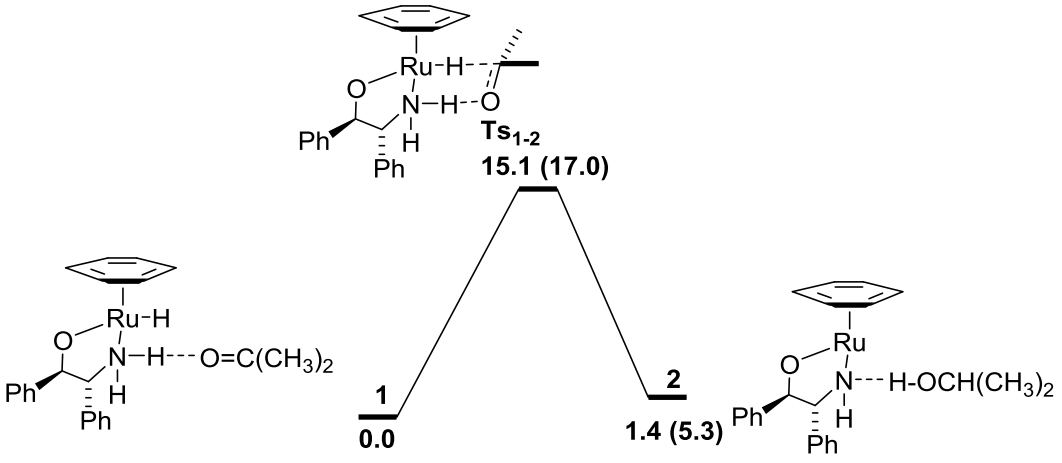


Figure 17. ATH of acetone gas phase modelling.[1]

1. $\Delta E(\Delta G°_{298K})$kcal/mol

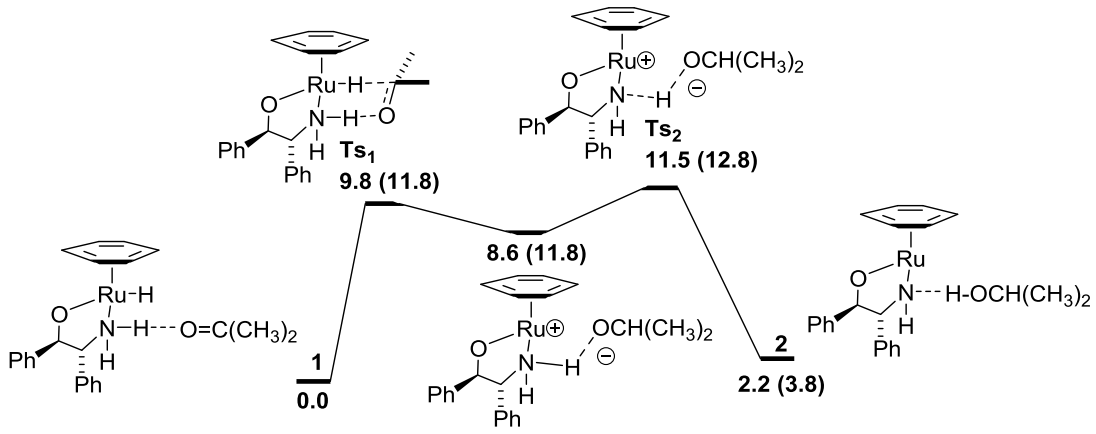


Figure 18. ATH of acetone continuum solvent reaction field solvation modelling.[1]

1. $\Delta E(\Delta G°_{298K})$kcal/mol

Introduction of explicit solvent molecules into the calculations further stabilizes the proton transfer step. Compared to the gas phase and non-solvent solvation modelling, the incorporation of one molecule of isopropanol will decrease the energy barrier of each step. This is especially the case in the transition states of proton transfer (**Ts2a** and **Ts2b** in **Figure 19**); the incorporation of one or two molecules of isopropanol will significantly decrease the energy of **Ts2a** and **Ts2b** which makes the hydride transfer the highest energy step.

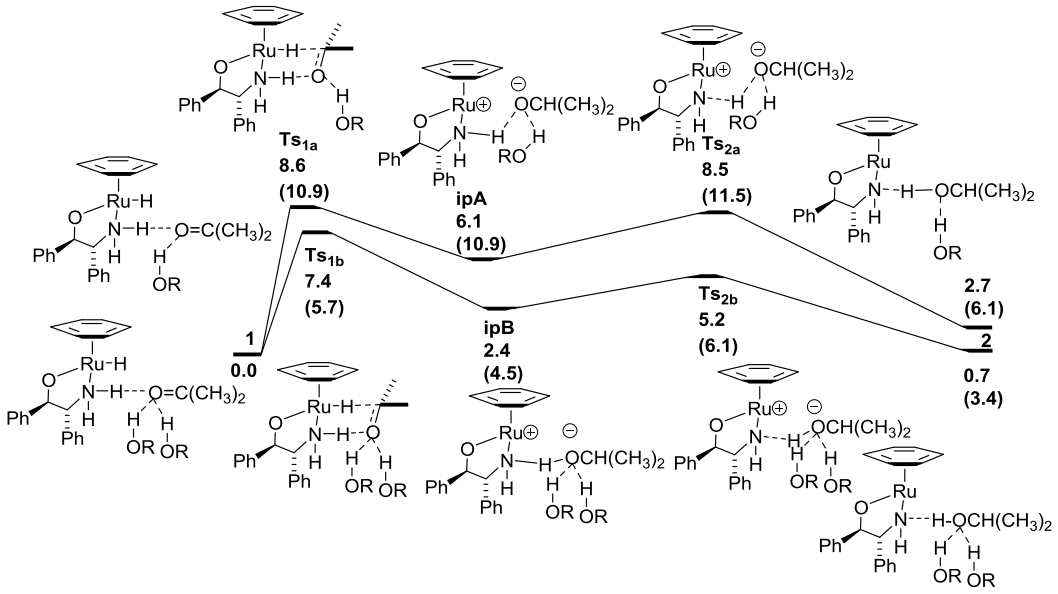


Figure 19. ATH of acetone continuum solvent reaction field solvation modelling + explicit solvent.[1, 2]

1. $\Delta E(\Delta G°_{298K})$kcal/mol.

2. R=isopropyl

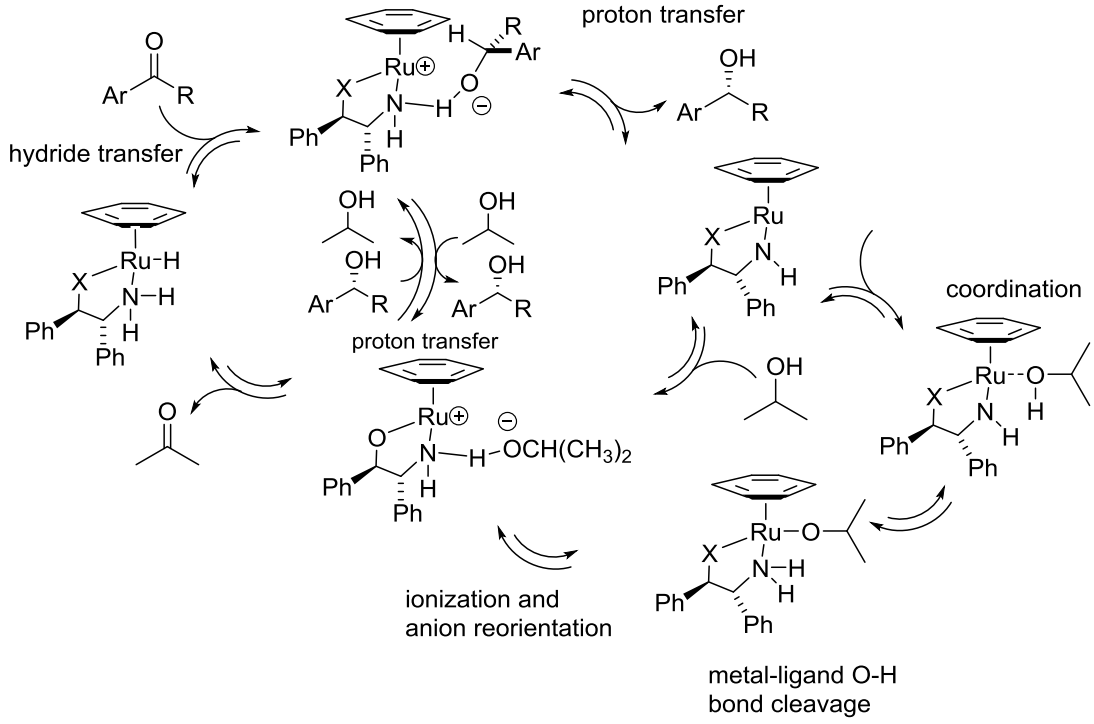


Figure 20. Revised catalytic cycle of asymmetric transfer hydrogenation.

Based on the present work and the overall experimental and theoretical data accumulated so far, Ikariya and co-workers proposed a revised catalytic cycle of asymmetric transfer

hydrogenation. The first step is the enantio-determining hydride transfer from the neutral amine which is also rate-determining. The second step is the formation of the ion pair by reaction with the solvent molecule and then the product is released. The sixteen electron amido-Ru complex becomes coordinated to isopropanol and forms the isopropyloxo-Ru complex through a metal-ligand O-H bond cleavage. Through ionization and anion reorientation the ion pair intermediate is then formed. The hydride regeneration from isopropanol can be recognized as the reverse reaction of hydride transfer. After release of acetone the catalytic cycle is closed.[42]

1.2.5. Iridium, Osmium and Iron Based Catalysts in ATH of Ketones.

Although the majority of reported ATH reactions require the use of ruthenium, enantioselective transfer hydrogenation based on iridium, osmium and iron catalysts has also been investigated. Novel ligands that have been found to not be efficient in ruthenium catalysed transfer hydrogenation have demonstrated immense power in iridium and other metal-catalysed transfer hydrogenation.[43]

A range of ligands were used in the Ir catalysed ATH of ketones. Before the development of 1,2-diamine ligands, bidentate ligands such as imine-pyridine,[25] bi(2-oxazoline)[26] and diphosphine[44] were used for ATH of ketones. Although those catalysts could offer high catalytic reactivity at elevated temperature ($\geq$ 80 °C) the lack of applications at room temperature and the relatively low and variable enantioselectivity are still problems that chemists have to face. Tosylated 1,2-diamine ligand was first intruded by Lemaire[45] in the ATH reaction of acetophenone **13** at room temperature (**Figure 21**). This catalyst could be formed in *situ* and used at room temperature with a slight increase of enantioselectivity compared to the pyridine, bi(2-oxazoline) and diphosphine ligands mentioned earlier.

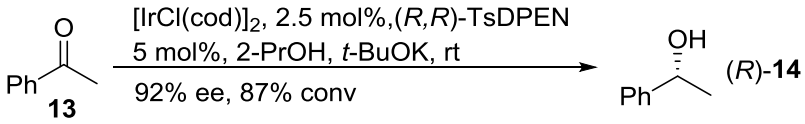


Figure 21. Ir catalysed ATH of ketones using TsDPEN as ligand.

By following these ideas, more chiral 1,2-diamine based ligands were discovered and applied to the field of ketone transfer hydrogenation. These include complex **38** (up to 93% ee for aryl ketone ATH),[46] **39** [IrCl(Cp*){(*R,R*)-TsCYDN }] (94-96% ee for aryl ketone ATH)[47] and **40** [IrCl(Cp*){(*R,R,R*)-CsDPEN}] (85-98% ee for aryl ketone ATH)[48] which are very active as well as enantioselective. With regard to the non-functionalized aromatic ketone reduction, more catalysts have been reported, including polymer-supported IrCl(Cp*)-diamine catalyst,[49] proline-based hydroxamic acid-$[IrCl_2(Cp^*)]_2$ complex,[50] quinine and cinchonine derivatives-$[IrCl(cod)]_2$[51] and diamino[bis(thiophene)][Ir(cod)(PPh_3)],[52] all of which work very well. Like Ru catalysts, isopropanol, formic acid and sodium formate are suitable as the hydrogen donor when Ir catalysts were used although triethylamine was not commonly involved.

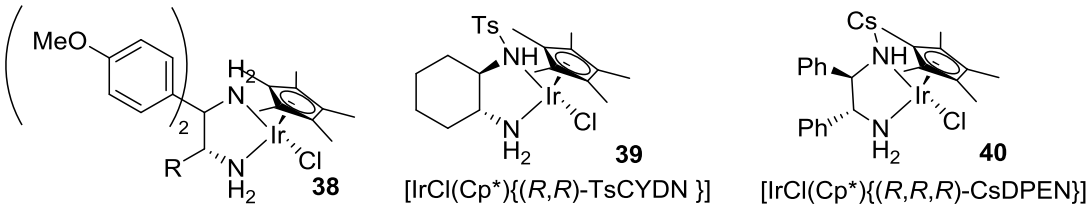


Figure 22. Different iridium catalysts for ATH.

Notably, iridium catalysts could also be used in the ATH of functionalized aromatic ketones. The catalyst **45** in **Figure 23** was employed by Carreira and co-workers[53] for the reduction of α-cyano and α-nitro ketones. From the experimental results α-cyano and α-nitro ketone could not only tolerate the reaction conditions but also were reduced with excellent enantioselectivity. In particular, it was found that the use of electron-poor ligands enhanced enantioselectivity and catalytic activity.

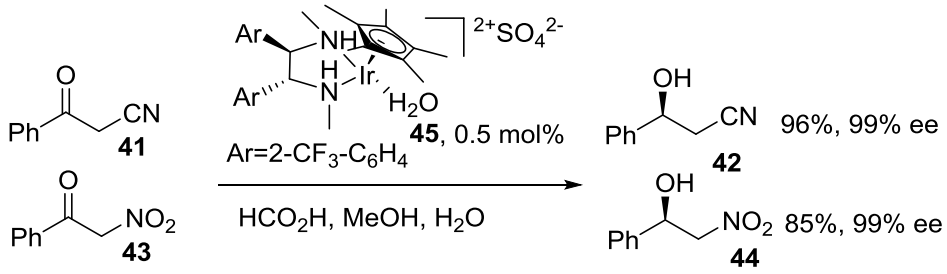


Figure 23. ATH of functionalized aromatic ketones by Ir catalyst.

Less widely used osmium catalysts are also able to catalyze transfer hydrogenation of carbonyl compounds in an enantioselective manner. For example, Os-pybox-phosphite complexes (**Figure 24**) were reported to be active as well as stereoselective for transfer hydrogenation. Good to excellent ee values (55-94%) were achieved but this catalytic system is less efficient than Ru catalysts and needs to be carried out at 82 °C.[54]

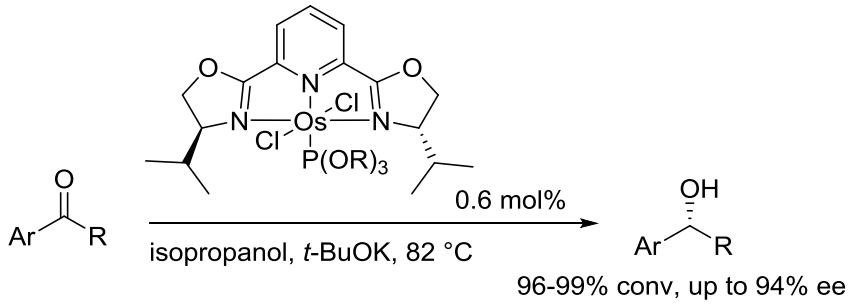


Figure 24. Osmium catalyzed ATH reaction.

Fe complex *trans*-[Fe(CO)(NCMe)-($PPh_2CH_2CHNCHPhCHPhNCHCH_2PPh_2$)]$(BPh_4)_2$ **46** was found to be extremely active as well as stereoselective in transfer hydrogenation of aromatic ketones (**Figure 25**).[55] This transfer hydrogenation catalyst could reach average TOFs of 2000-3000/h in isopropanol at 22 °C compared to the most efficient asymmetric hydrogenation catalyst (TOF 4000/h) in the same solvent. Good to excellent enantioselectivities were achieved when the substrates were aromatic ketones. The catalyst was equally active towards aliphatic ketones but the enantioselectivities were significantly lower.

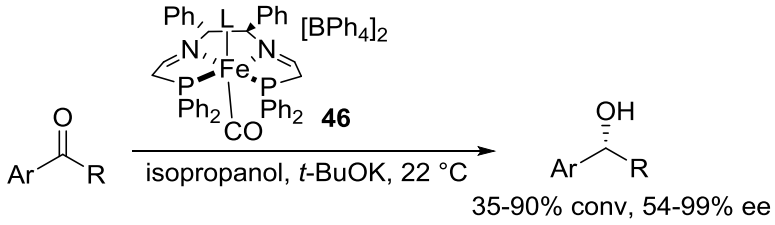


Figure 25. Iron catalyzed ATH reaction.

1.2.6. Asymmetric Transfer Hydrogenation of Diketones, Keto Esters and Dynamic Kinetic Resolution.

1.2.6.1. ATH of α-Keto Esters and 1,2-Diketones.

Aromatic α-keto esters have been recognized as activated ketones and their asymmetric transfer hydrogenation was first reported by the Mohar group (**Figure 26**). An array of ligands has been tested and the screening suggested the more hindered RSO_2N group could offer better enantioselectivity. This may be due to the high activity of α-keto esters as the enantioselectivities were lower than unactivated ketones (average 70-90% ee).[56]

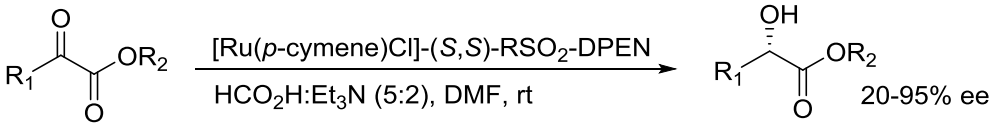


Figure 26. ATH of α-keto esters in organic solvent.

Aromatic α-keto esters are good substrates for asymmetric transfer hydrogenation. Following the ATH study of α-keto esters in organic solvents by Mohar, Li's group published another α-keto ester reduction under aqueous conditions and with a (*R*,*R*)-2,4,6-triisopropyl-$C_6H_2SO_2$-DPEN ligand (**Figure 27**).[57] ATH of α-keto esters in water with the cationic surfactant (DTAB, dodecyl trimethyl ammonium bromide) is faster than in organic solvent and by using this ligand the average ee values were around 80-90%. With more evidence collected for the ATH of aromatic α-keto esters, it was found that the general ee values were lower than other aromatic ketones. In some extreme examples,

even in the reduction of aromatic ketones the enantioselectivities were still low (R_1=2,4,6-trimethylphenyl, 35% ee; R_1=2-methoxyphenyl, 34% ee).

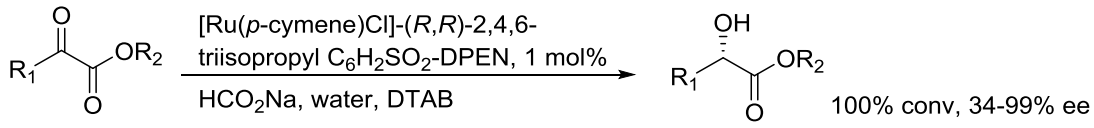


Figure 27. ATH of α-keto esters in water.

In 2009, Zhang reported an asymmetric transfer hydrogenation of α-keto pantolactam, by using Noyori's [Ru(*p*-cymene)Cl]-(*R*,*R*)-TsDPEN] catalyst [(*R*,*R*)-**c1**] (**Figure 28**). According to his publication, a simple, efficient, and highly enantioselective method was developed and more than 2 kg of this key intermediate has been synthesized in excellent chemical yield and optical purity.[58]

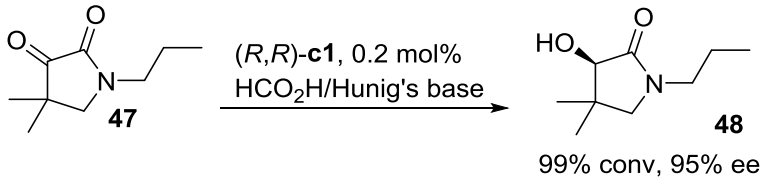


Figure 28. ATH of α-keto pantolactam.

1.2.6.2. ATH of β-Keto Esters and 1,3-Diketones.

Asymmetric transfer hydrogenation of β-keto esters was first reported by the Carpentier group in 1998. By using $[RuCl_2(\eta^6\text{-arene})]_2$ and ephedrine or mono-tosylated diamine ligands the authors found that only aromatic β-keto esters could afford high enantioselectivities (**Figure 29**). According to the author if R_1 equals Me or CH_2OMe then no matter what R_2 group is used the enantioselectivity will be disappointingly low (**Figure 29**).[59]

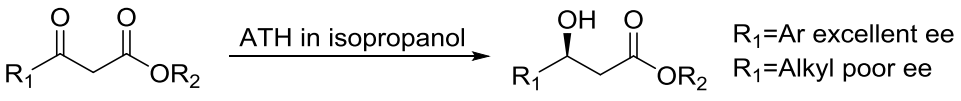


Figure 29. The first report of the ATH of β-keto esters.

Asymmetric transfer hydrogenation of β-keto esters can be carried out in an emulsion (water/CH_2Cl_2) system with more accelerated turnover rate than in water. The authors suggested that when the ketones are in solid form or have limited solubility in water, emulsion is the solution in which reaction reactivity was enhanced but enantioselectivity was maintained at the same level (**Figure 30**).[60]

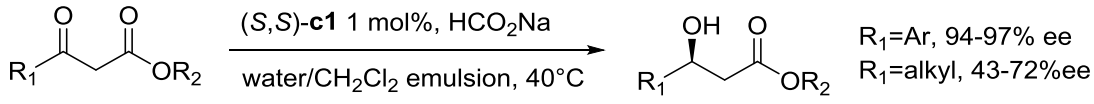


Figure 30. ATH of β-keto esters in emulsion.

Diastereoselective asymmetric transfer hydrogenation of chiral aliphatic 4-hydroxy-2-keto esters is ambitious. According to the paper published by Carpentier,[61] substrates were reduced successfully but diastereoselectivities were quite unpredictable; not only were de values poor, but in some examples just changing the structure of the arene will turn the major product from *syn* to *anti*. All the efforts to improve de by changing the structure of ligands, arene and R groups were all in vain and the widely applied **c1** catalyst has proved to be totally inefficient in this system (**Figure 31**).

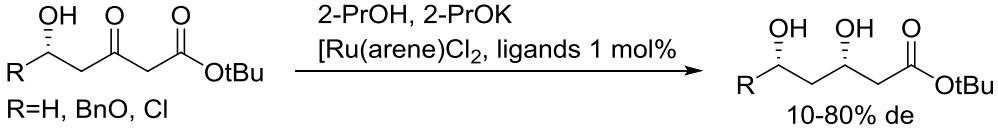


Figure 31. ATH of chiral β-keto esters.

Asymmetric transfer hydrogenation of 1,3-diketones was first reported by the Cossy group.[62] Under optimized conditions, good diastereo- and enantioselectivities could be achieved when R_1=R_2=Ar (up to 98.5/1.5 dr and 99.5% ee), if R_1 or R_2 equals alkyl then the ee and dr will decline substantially. Unlike other ketones, 1,3-diketones are not quite active at room temperature therefore elevated temperatures and high catalyst loadings were required for complete conversion.

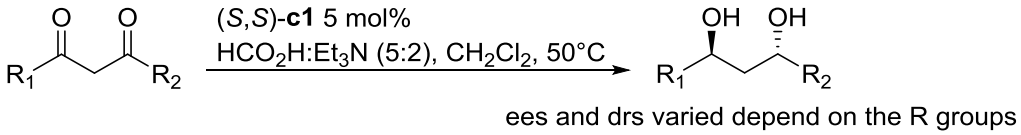


Figure 32. ATH of 1,3-diketones.

1.2.6.3. Asymmetric Transfer Hydrogenation Dynamic Kinetic Resolution.

α-Substituted ketones, due to their low pKa values have been discovered to be good substrates for dynamic kinetic resolution. The Wills group reported the dynamic kinetic resolution of a group of structurally novel α-substituted ketones. In general good to excellent ees and des were achieved even in the case of non-aromatic ketones (**Figure 33**).[63]

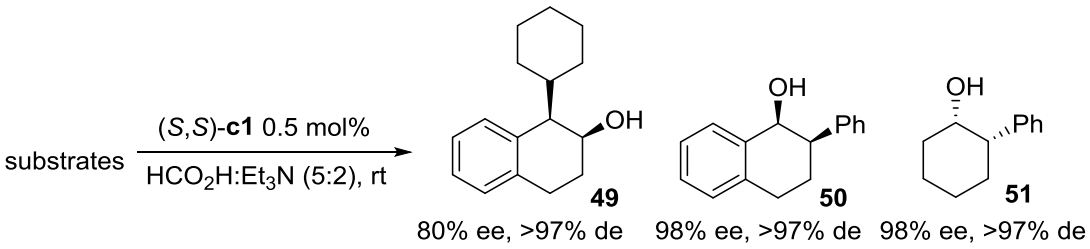


Figure 33. DKR of α-substituted ketones.

Not only restricted to β-keto esters, β-keto amides, or other substrates with only one ketone group, 1,3-diketones are applicable to dynamic kinetic resolution methods as well. Cossy et al. reported a group of novel 2-alkyl-1,3-diketones which could be used in mono-reductive dynamic kinetic resolution (**Figure 34**).[64] The catalyst can recognize the less steric hindered therefore more active carbonyl and reduce it in a both diastereo- and enantioselective manner. The method is only applicable to diketones in which the two carbonyls have different reactivity. If the two carbonyls have similar reactivity, enantioselectivity will decrease which also result inseparable mixed products.

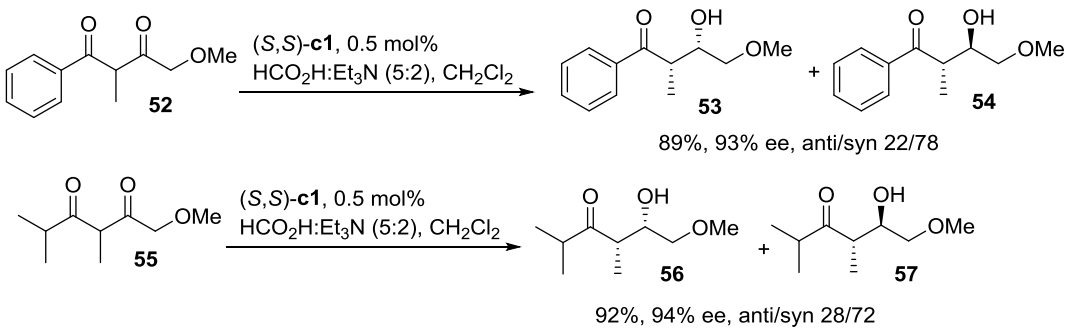


Figure 34. DKR of 1,3-diketones.

Racemic benzoin is a good substrate for dynamic kinetic resolution. In 1999, Ikariya published a very efficient route for the large scale synthesis of chiral 1,2-diols by a dynamic kinetic resolution. The ee value of the product chiral 1,2-diol **59** could be further enhanced by recrystallization. Notably compound **58** is not easily reduced by currently available direct hydrogenation catalysts (**Figure 35**).[65]

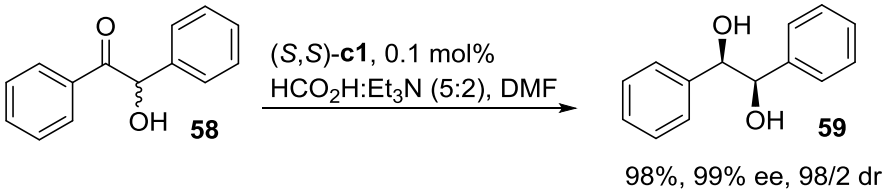


Figure 35. DKR of α-hydroxyl ketones.

A very efficient dynamic kinetic resolution of ethyl 2-benzamidomethyl-3-oxo-4,4,4-trifluorobutanoate **60** was applied to access the *syn*-enriched chiral compound at the early synthetic stage of the synthesis of the *anti*-bacterial substances Sanfetrinem and LK-157. The authors claim that low concentration of substrate and small η^6-arene size of the catalyst was detrimental for high diastereoselectivity. Using Ru(mesitylene) the diastereoselectivity (*syn/anti* 94/6) of dynamic kinetic resolution turns out to be very high as well as the enantioselectivity (>99% ee). After a recrystallization the de value of **61** was determined to be >99% (**Figure 36**).[66]

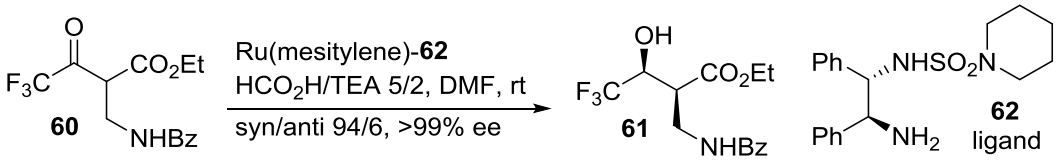


Figure 36. DKR of α-substituted-γ-trifloro-β-keto ester.

Dynamic kinetic resolution of 2-methoxy-3-oxo esters has been reported by the R-Vidal group.[67] During the screening of catalysts the authors discovered that dr values are determined by the arene of catalyst rather than the substituents on the diamine ligands. When the arene was 1,3,5-trimethylbenzene, products were formed with the maximum dr values. They also found that dr values were independent of temperature or solvent. In their substrate screen, with the exception of R_1=2-bromophenyl (2.5/1 dr), all other products including R_1=(*E*)-phenylvinyl were formed in drs higher than 24/1 (**Figure 37**).

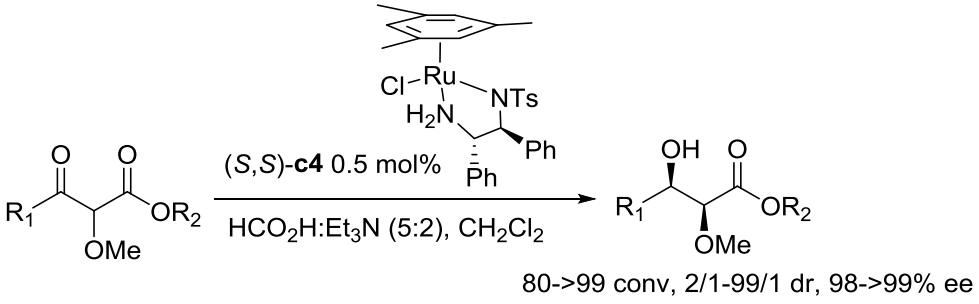


Figure 37. DKR of α-methoxyl-β-keto esters.

Recently the Yawen group published the dynamic kinetic resolution of 2-chloro-3-oxo esters by using (*S*,*S*)-**c1** catalyst in HCO_2H/Et_3N 5/2 mixture.[68] In contrast to the results described in **Figure 37**, 2-chloro-3-oxo esters as the starting material did not yield products in good diastereoselectivity (**Figure 38**). According to the authors, the dr values are not dependent on catalyst loading but heavily on the substitution on the aromatic ring. Modest to good drs and ees were obtained under optimized conditions suggesting that 2-chloro-3-oxo esters might not be the ideal substrates for ATH dynamic kinetic resolution. In this paper only one catalyst was tested therefore an understanding of the nature of the relationship between structure of catalysts and drs or ees of products is still elusive.

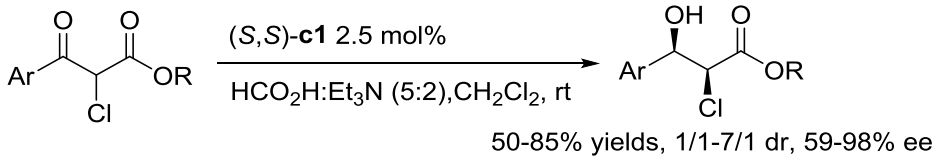


Figure 38. DKR of α-chloro-β-keto esters.

Dynamic kinetic resolution of β-keto sulfones with HCO_2H/Et_3N 5/2 was reported by the Zhang group in 2008. Excellent enantioselectivities and diastereoselectivites were achieved by using (*S*,*S*)-**c1** catalyst when substrates were aromatic β-keto sulfones. The author demonstrated that the reaction worked equally well when performed in CH_3OH, CH_3CN and DMSO but slower when in THF and toluene. For some reason, 2-substitution of the aryl will jeopardize both the ee and dr values. The reduction system is extremely substrate dependent; for example if Ar=4-methoxyphenyl the yield will drop to <5% and ee were generally low when aliphatic β-keto sulfones were tested (**Figure 39**).[69]

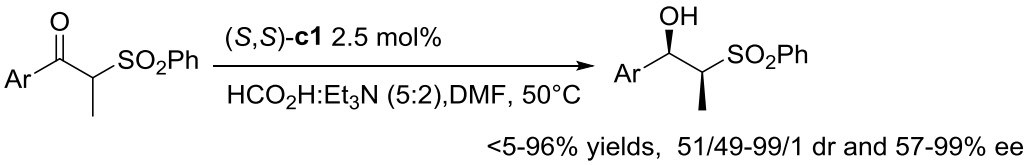


Figure 39. DKR of β-keto sulfones.

Dynamic kinetic resolution of α-alkyl-β-keto amides was first published by Krska.[70] The products, chiral α-alkyl-β-hydroxyl-amides are ideal starting materials for lactam synthesis. By using the catalyst shown in **Figure 40** good to excellent enantioselectivities and diastereoselectivities could be achieved. The authors expanded the scope of substrates by changing the R_2 group and the results demonstrate that both enantioselectivity and diastereoselectivity are not strictly affected by the size of the R_2 group.

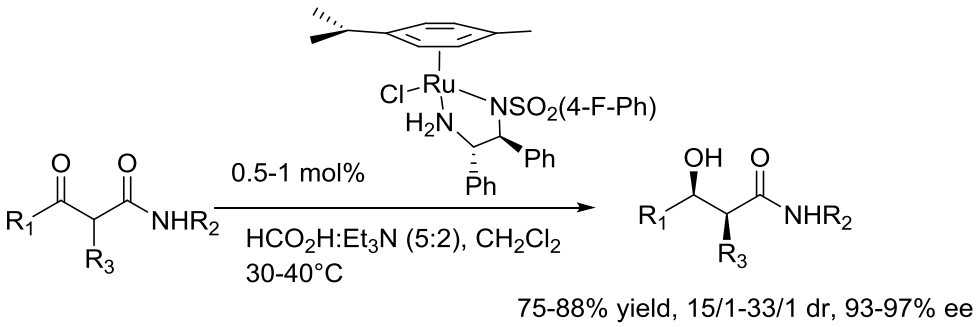


Figure 40. DKR of α-alkyl-β-keto amides.

Transfer hydrogenation has been used in the dynamic kinetic resolution of β-aryl-α-keto esters and β-amino-α-keto esters by the Johnson group recently.[71] The starting material can be obtained on a multi-gram scale therefore this offers a good opportunity for application to a synthetic target. In this paper the author described synthesis of chiral β-aryl-α-hydroxy-esters and γ-butyrolactones by dynamic kinetic resolution. From ligand screening the results showed that TsDPEN was inefficient for the DKR of α-keto esters (57/43 er). Increasingly, the large size of the Ar group of the diamine and the R group of the sulfonamide has beneficial effects on enantioselectivity (**Figure 41**).

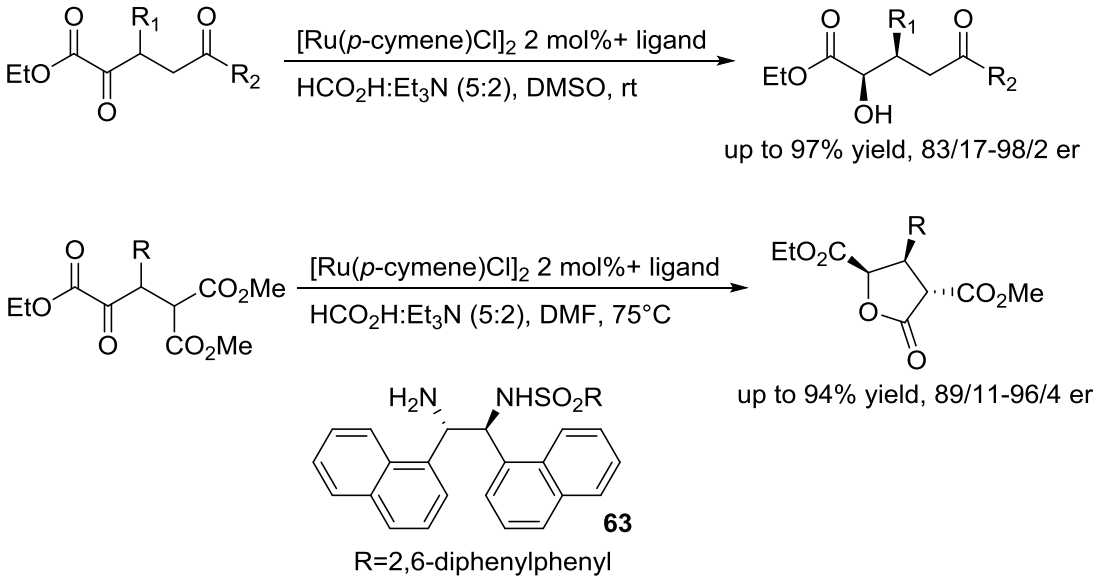


Figure 41. DKR of β-aryl-α-keto esters and lactone formation.

Another application of dynamic kinetic resolution of β-amino-α-keto esters was also published by the Johnson group recently.[72] Starting material; β-amino-α-keto esters are

readily available from the corresponding α-diazo-β-amino-esters. This paper also proved that the increase of the size of Ar group of the diamine has a beneficial effect over dr values. Both enantio- and diastereoselectivities were highly dependent on the nature of the R group. If the R group was aromatic, both enantio- and diastereoselectivity were high; if the R group was an alkyl group then the enantio- and diastereoselectivity decreased dramatically (e.g for CH_2Bn the dr and er drops to 3/1, 59/41 respectively) (**Figure 42**).

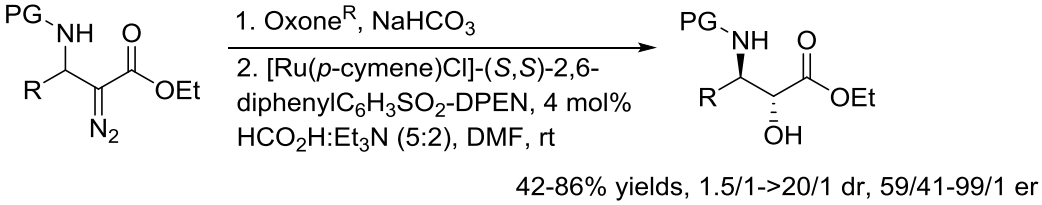


Figure 42. DKR of β-amino-α-keto esters.

1.2.7. Asymmetric Transfer Hydrogenation of Propargylic Ketones.

Soon after the publications on the ATH of aromatic ketones, Noyori reported the asymmetric transfer hydrogenation of propargylic ketones by using the same ruthenium catalyst **c1** and isopropanol as hydrogen donor.[73] This method allows reduction of structurally diverse propargylic ketones to propargylic alcohols with high enantiomeric purity whilst leaving the C≡C bond intact. This reaction is characterized by high yields, excellent enantioselectivities and low catalyst loadings (0.5 mol%), has become a major and powerful pathway to access chiral propargylic alcohols and has been widely applied to natural product synthesis (**Figure 43**).

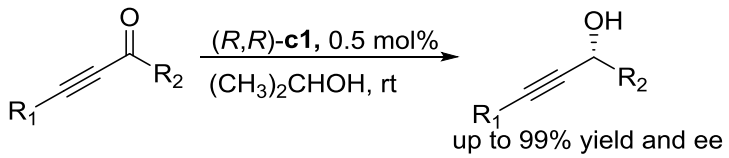


Figure 43. ATH of propargylic ketones.

After Noyori's publication, asymmetric transfer hydrogenation of propargylic ketones has proven to be a reliable method for the synthesis of chiral propargylic alcohols. More often than not it has been used as a key transformation in target related synthesis. However a full and detailed picture of the general behaviour of propargylic ketones in transfer hydrogenation is still elusive.

In 2011, Cossy published a diastereoselective transfer hydrogenation of chiral α,β-epoxy and α,β-aziridinyl ynones. In this letter, the structures of chiral α,β-epoxy, α,β-aziridinyl and the absolute configuration of catalysts ((*R*,*R*)-**c1** or (*S*,*S*)-**c1**) were demonstrated to have a significant effect on the diastereoselectivity, and this was discussed in detail (**Figure 44**).[74] The author also elucidated how different adjacent functional groups on substrates could affect the stabilities and diastereoselectivities in catalytic transfer hydrogenation.

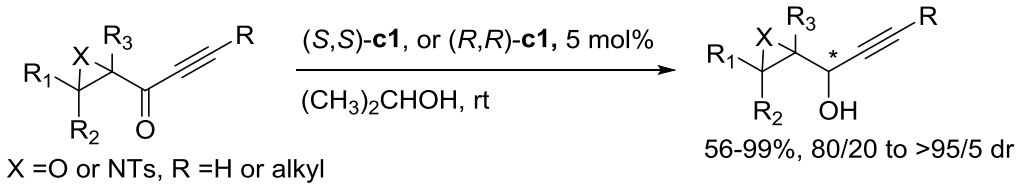


Figure 44. ATH of α,β-epoxy and α,β-aziridinyl ynones.

To access chiral aliphatic secondary alcohols; a one-pot catalytic asymmetric transfer hydrogenation-hydrogenation process was also developed by the Cossy group. Catalyst (*R*,*R*)-**c1** and $Pd/BaSO_4$ were introduced sequentially to first reduce the carbonyl of the ynone and then the triple bond (**Figure 45**).[75] Interestingly, formic acid was used as the hydrogen source for both transfer hydrogenation and hydrogenation. Side reactions such as Pd catalysed redox reaction generated traces of saturated ketone and therefore will cause the erosion of ee values. Compared to other hydrogenation catalysts ($Pd(OH)_2/C$, $PdCl_2$, $Pd(acac)_2$ and Pd/C), $Pd/BaSO_4$ can potentially offer the highest yields and was therefore chosen for the stage two reduction.

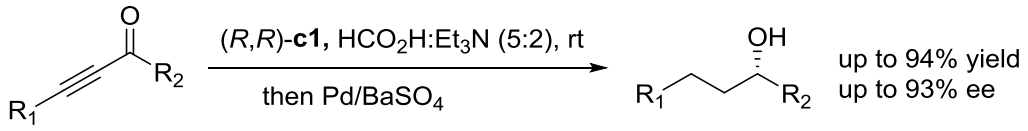


Figure 45. One-pot ATH and hydrogenation of propargylic ketones.

The three examples above constitute a summary of systematic asymmetric transfer hydrogenation studies on propargylic ketones. Although there are several applications in natural product synthesis, these routes generally introduced without any major change to the catalyst structures or reaction conditions. The method of asymmetric transfer hydrogenation of propargylic ketones has been widely used in natural product total synthesis and in most cases Noyori's method[73] has been applied without optimization. In the following chapter a range of functionalized propargylic ketones were reduced by ATH to demonstrate the efficiency and power of Noyori's asymmetric transfer hydrogenation in natural product total synthesis.

1.2.8. ATH of Propargylic Ketones: Applications to Total Synthesis of Natural Products.

Asymmetric transfer hydrogenation of propargylic ketones to generate chiral propargylic alcohols serve as a convenient method which has received broad application in the total synthesis of natural products. Usually this is used as a key step and provides a reliable way to introduce a hydroxyl group into the skeleton of natural products. To date this method has been applied by a number of synthetic groups. For example (**Figure 46**) the formal synthesis of phoslactomycins and leustroducsins by the Cossy group from chiral compound **64** and **65** obtained from ATH,[76] the total synthesis of fostriecin by the Trost group from diol **66**,[77] the synthesis of pentacyclic lycopodium alkaloid huperzine Q from starting material **67**[78] and the *de novo* total synthesis of macrolides cladospolide B-D from propargylic alcohol **69**.[79]

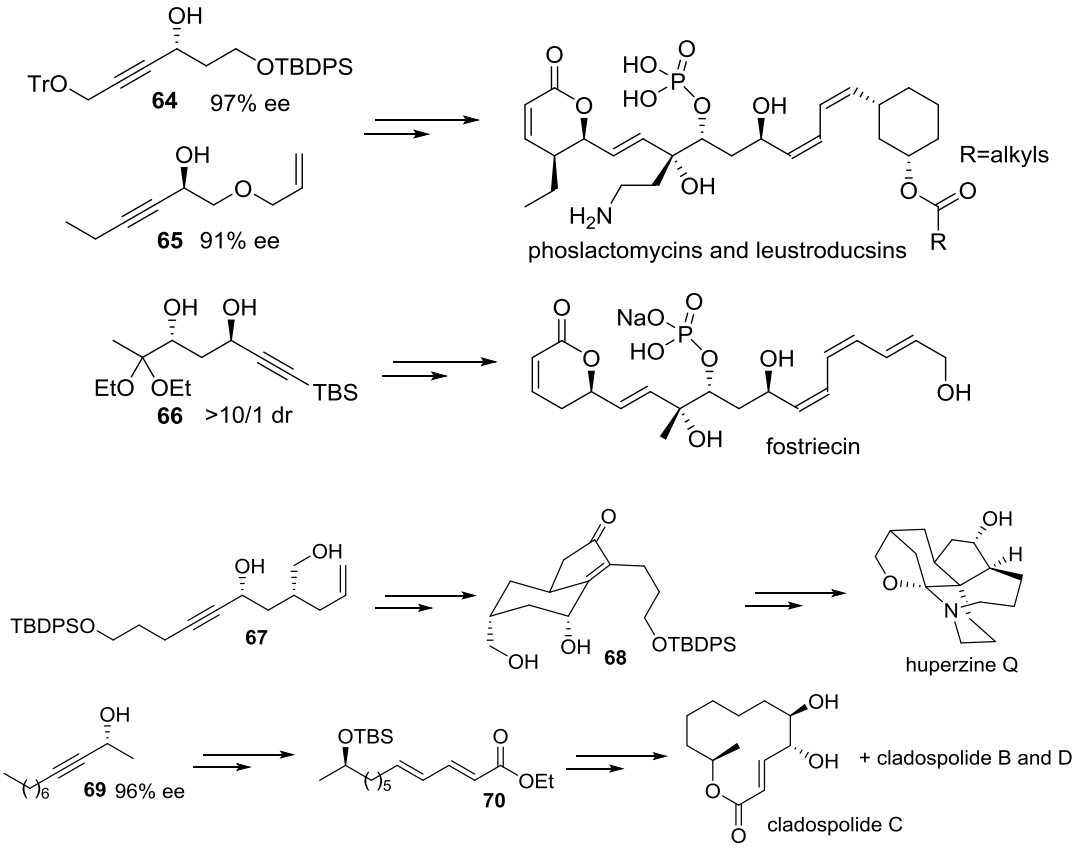


Figure 46. ATH in total synthesis of natural products.

1.3. Asymmetric Reduction of Propargylic Ketones.

Before the enantioselective catalytic method discussed above, chiral Alpine borane was widely applied to the reduction of conjugated ynones (**Figure 47**).[80] Yields and selectivities varied depending on the structural differences of the ynones. The range and scale of this transformation are limited due to (1) the high cost of (+)/(-)-Alpine borane (2) the requirement of stoichiometric loadings (3) specific structural requirements of substrates; but still important in small-scale target related synthesis.

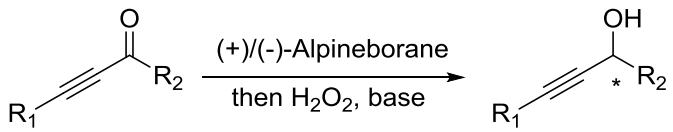


Figure 47. Asymmetric reduction of ynones by chiral Alpine borane.

A (L)-TarB-NO_2 **71** and sodium borohydride mediated asymmetric reduction of α,β-propargylic ketones was developed by the Singaram group.[81] In this publication a range of propargylic ketones were tested but only highly branched aliphatic ynones could reach up to 90% ee, whilst reduction of aromatic and linear aliphatic ynones led to only poor to modest enantioselectivity (6-58% ee) (**Figure 48**). Furthermore, the use of (L)-TarB-NO_2 as ligand to control the enantioselectivity required its use in stoichiometric amounts (1 equiv).

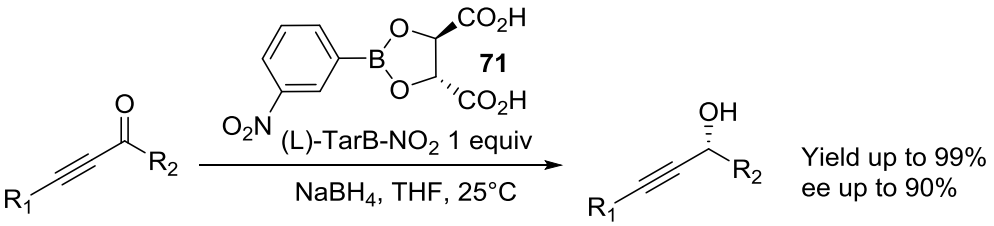


Figure 48. Asymmetric reduction of ynones by (L)-TarB-NO_2 and sodium borohydride.

The asymmetric reduction of prochiral γ-acetylenic-β-keto ester **72** to the corresponding alcohol **73** with bakers' yeast was first reported by Hiyama (**Figure 49**).[82] The selectivity of baker's yeast reduction is dependent on the size difference of groups on the each side of the carbonyl group of the substrate. Because the enantioselectivity is only moderate in most cases this method has not been widely applied in target related synthesis.

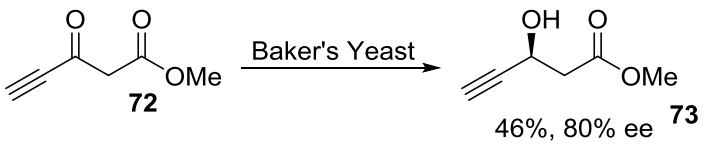


Figure 49. Asymmetric reduction of propargylic ketone by baker's yeast.

1.4. Synthesis of 6-(2-Hydroxy-2-alkyl(aryl)ethyl)-2,2-dimethyl-4H-1,3-dioxin-4-ones.

Using literature methods, 6-(2-hydroxy-2-alkyl(aryl)ethyl)-2,2-dimethyl-4H-1,3-dioxin-4-ones (**Figure 50**) can be prepared both in racemic and enantio-enriched manner from a variety of reactions.

To form the racemic compound the procedure is relatively simple. There are two methods: (1) lithium enolate attack on aldehydes (**Figure 50**); (2) vinylogous Mukaiyama reaction (**Figure 51**); both of which have been applied to obtain 6-(2-hydroxy-2-alkyl(aryl)ethyl)-2,2-dimethyl-4H-1,3-dioxin-4-ones.

The most convenient and straightforward approach is by lithium enolate attack (**Figure 50**).[83] Lithium enolate is first formed by LDA deprotonation of 2,2,6-trimethyl-1,3-dioxin-4-one **74** and the *in situ* generated reagent is used straight away to couple with aldehydes. This method was also adopted in this project to form racemic samples (see later sections).

Figure 50. Preparation of 6-(2-hydroxy-2-alkyl(aryl)ethyl)-2,2-dimethyl-4H-1,3-dioxin-4-ones by lithium enolate attack.

The vinylogous Mukaiyama reaction has also been applied to the synthesis of 6-(2-hydroxy-2-alkyl(aryl)ethyl)-2,2-dimethyl-4H-1,3-dioxin-4-ones. A variety of reaction conditions and catalysts have been investigated. These include the $TiCl_4$[84] and silicon tetrachloride[85] ($SiCl_4$) promoted Mukaiyama reactions. Those reactions generally have to be run under anhydrous condition although a $Bi(OTf)_3 \cdot 4H_2O$[86] catalyzed Mukaiyama addition developed by Scettri is not so moisture sensitive (**Figure 51**).

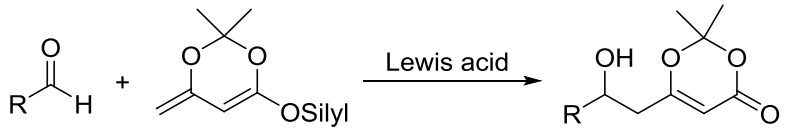


Figure 51. Preparation of 6-(2-hydroxy-2-alkyl(aryl)ethyl)-2,2-dimethyl-4H-1,3-dioxin-4-ones by vinylogous Mukaiyama reaction.

The asymmetric synthesis of chiral 6-(2-hydroxy-2-alkylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-ones was first reported by Chikara by using a Mukaiyama aldol reaction.[87] A novel tartaric acid derived acyloxyborane complex **75** was applied as the catalyst. Aliphatic, aromatic and vinyl aldehydes were tested and the result shows that the ee values were largely independent of the substrate structure; moderate ee values (62-73% ee) and yields (44-84%) were achieved (**Figure 52**).

Ti^{4+} and Cu^{2+}((*S*)-Tol-BINAP/CuF_2) Lewis acid complexes **77** were discovered by Carreira in 1995 and 1998 respectively.[88] Those catalysts exhibit unprecedented high enantioselectivities (up to 99% ee) and catalytic reactivities (1-3 mol% loading) in the vinylogous Mukaiyama reaction with aldehydes. The reactions are applicable to both aliphatic, aromatic, vinyl aldehydes and propargylic aldehydes without erosion of enantioselectivity. But to get pure product, an acidic work-up was required because of silyl migration which will increase the complexity of manipulation. A [Cu(*S*,*S*)-Ph-pybox]$(SbF_6)_2$ catalysed asymmetric Mukaiyama reaction was developed by the Evans group.[89] This catalyst can be generally applied to a broad range of enol silyl ethers and dienol silyl ethers. To the silyl ether described in **Figure 52**, only one example has yet been demonstrated to work with good yield and ee (94%, 92% ee, 5 mol% catalyst).

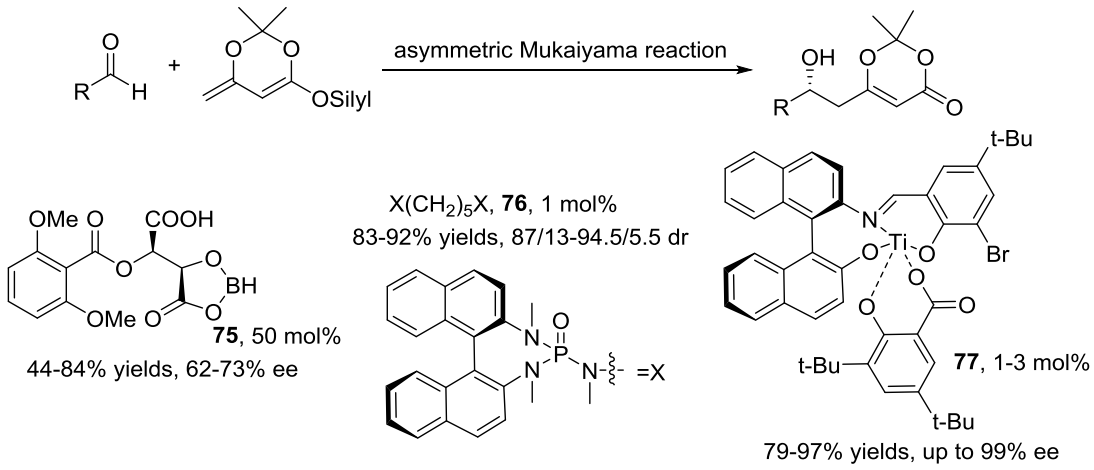


Figure 52. Catalytic entantioselective synthesis of 6-(2-hydroxy-2-alkylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-ones.

More catalytic Mukaiyama-type reactions have been published (see **Figure 52** for general procedure). Scettri reported a Ti(O*i*-Pr)$_4$/(*R*)-BINOL complex which can be applied to both aliphatic and aromatic aldehyde substrates. In his report, enantioselectivities for aromatic aldehyde substrates were higher than for aliphatic (97->99% ee versus 89-92% ee).[90]

The Denmark's group discovered that the combination of a catalytic amount of the chiral bis-phosphoramide **76** and silicon tetrachloride is able to promote a highly enantioselective and diastereoselective addition of silyl enol ether to aldehydes.[91] This method is highly efficient, and good to excellent dr values and yields were achieved even at a loading of bis-phosphoramide catalyst as low as 1 mol% (**Figure 52**).

1.4.1. Applications of 6-(2-Hydroxy-2-alkylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-ones.

Katritzky[92] demonstrated that the 1,3-dioxin-4-one ring can be opened under high temperature or UV irradiation conditions to release acylketene intermediate through a retro-Diels-Alder mechanism. The acylketene intermediate has a strong affinity to

electron-rich substrates and therefore can serve as a scavenger of nucleophilic reagents such as alcohols, amines and thiols to generate β-keto esters, β-keto amides or β-keto thioesters. The reaction in **Figure 53** is the most commonly used application of 1,3-dioxin-4-one and has been used widely in natural product total synthesis.

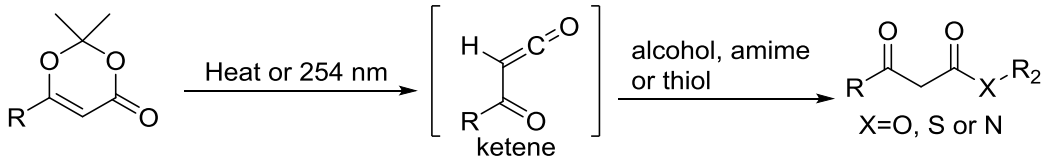


Figure 53. Ring open of 1,3-dioxin-4-one.

There are some applications which include the reaction shown in **Figure 53**. The 1,3-dioxin-4-one scaffold was recognized as the precursor to β-keto esters and a range of structures can be prepared from this reaction. For example at an early stage of the synthesis of 3,5-deoxy amphotericin B methyl ester, the Carreira group treated compound **78** in *n*-butanol at 110 °C to release the β-keto ester **79** which could be further converted to acetonide 3,5-diol **80** (**Figure 54**).[93] Other applications of the thermal ring opening reaction to generate β-keto esters are all of the retro-Diels-Alder type.[94]

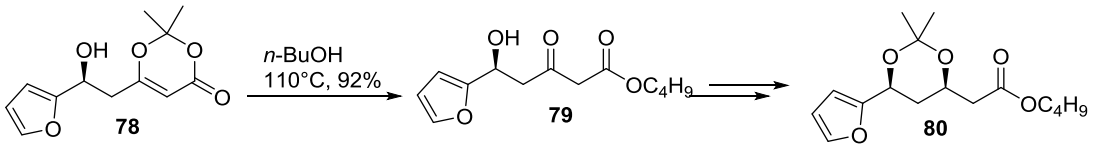


Figure 54. Application in total synthesis of natural products.

The Scheidt group reported the preparation of bicyclic compounds taking advantage of the embedded enol ether from the 1,3-dioxin-4-one core.[95] The 1,3-dioxin-4-one served as a nucleophilic reagent which can couple with aldehydes in a diastereoselective manner by a $Sc(OTf)_3$ promoted Prins cyclization (**Figure 55**). According to the authors, the diastereoselectivities are dependent on the R_2 groups of the aldehydes and during the cyclization no racemization was observed.

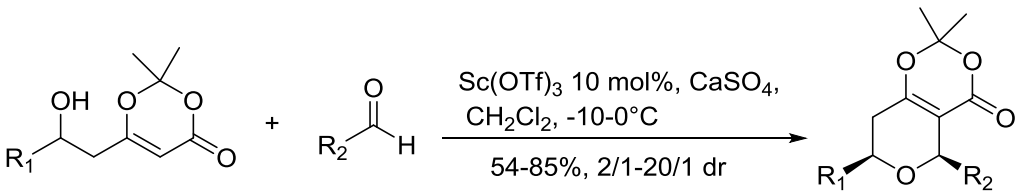


Figure 55. Prins cyclization reaction of 1,3-dioxin-4-one.

1.5. Chiral Diynols-Structure and Synthesis.

1.5.1. Structure of Chiral Diynols in Natural Products.

As a subclass of acetylenic natural product, diynols are unique structures found in many diacetylenic and polyacetylenic natural products.[96] In addition to their intriguing structure, this group of natural products is known to contain examples with highly potent anti-cancer and anti-HIV properties. However, the enantioselective syntheses of polyyne natural products are relatively rare due to the high instability of the polyyne unit.[97] Diynol natural products, their biological properties and total synthesis, will be discussed here.

The diynol natural products, strongylodiol A-C (**Figure 56**) were isolated from the sponge *genus Strongylophora*.[98] This group of compounds was found to contain most typically long-chain diacetylenic alcohols. Strongylodiols A-C possess cytotoxic activities against tumour cells (DLD-1 and MOLT-4), normal cells (IMR-90) and can be potentially used for anti-cancer treatment. Containing relatively simple structures, strongylodiols A-C are some of the most typical diynol compounds from nature. Several total syntheses of strongylodiol A and strongylodiol B have been published.[98]

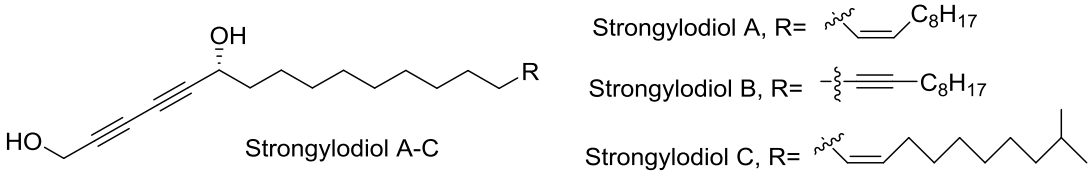


Figure 56. Structures of strongylodiol A-C.

Diynol natural products panaxjapyne A-C (**Figure 57**) were isolated as secondary metabolites from the roots of *Panax japonicus* C. A. Meyer var. major[99] alongside four other known compounds. The roots of *Panax* species have long been used either in Chinese traditional herbal medicine or for food in Asian regions. The roots of *Panax* species were prescribed as an expectorant, hemostatic, sedative, analgesic and antitussive medicine. It has also been found to be a rich source of C17 polyacetylene compounds. Potent yeast α-glucosidase activity inhibitory effects have been reported for these three new compounds. To date only a total synthesis of panaxjapyne C has been reported, using L-ascorbic acid as the source of chirality.[100]

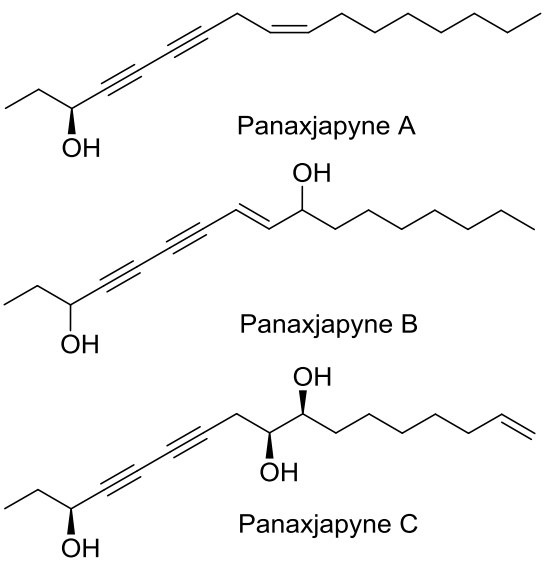
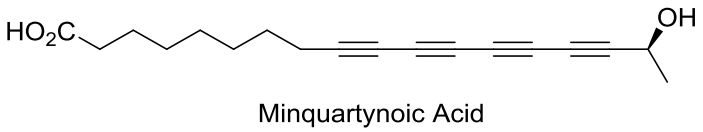


Figure 57. Structures of panaxjapyne A-C.

(*S*)-Minquartynoic acid (**Figure 58**) contains four contiguous triple bonds. This compound, isolated from the twigs of *ochanostachysamentacea* from Southeast Asia exhibits broad cytotoxicity against 10 different tumour cell lines. In Peru it was widely used as traditional medicine to cure malaria and leishmaniasis.[101]Although the total synthesis of (*S*)-minquartynoic acid has been published, the construction of notoriously unstable chiral polyynol is still challenging.[102]



Minquartynoic Acid

Figure 58. Structures of (*S*)-minquartynoic acid.

1.5.2. Synthesis of Chiral Diynols.

The structural diversity of diynols in nature makes access to this kind of building block of huge significance. The first 1,3-diyne asymmetric additions to aldehydes were reported by Carreira using a $Zn(OTf)_2$/*N*-methylephedrine ligand (**Figure 59**).[103] In the context of their total synthesis of (*R*)-strongylodiol A and B, asymmetric 1,3-diyne addition was used to introduce the chiral diynol functionality.

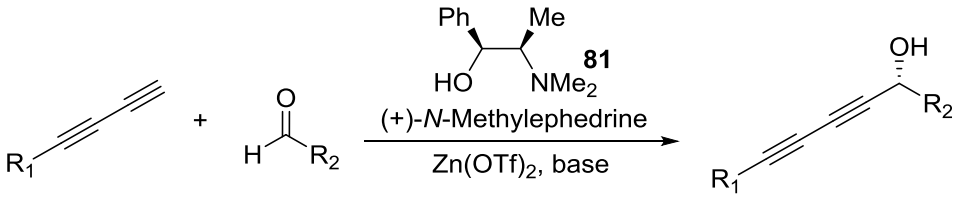


Figure 59. 1,3-Diyne asymmetric addition by Carreira's method.

The addition of 1,3-diynes to aldehydes has proved troublesome. (*R*)-Strongylodiol A and (*R*)-strongylodiol B were formed only in 62% yield/82% ee and 68% yield/80% ee respectively even when using a large excess of the ligand (4 equiv).[104] The long standing problem of this system is that when non α or β-branched aldehydes are used, the enantioselectivities typically drop to 70-88% ees. If α,β-unsaturated aldehydes are used, a competing Cannizaro reaction resulted in product formation in low yields (as low as 35%). Tykwinski also reported a modified method of Carreira's $Zn(OTf)_2$/*N*-methylephedrine protocol for the asymmetric addition of terminal di- and triynes to aldehydes.[105] Although the effects of reaction conditions have been fully investigated, including temperature, loading of $Zn(OTf)_2$, base and additives, this reaction is essentially still a non-catalytic one. To obtain good conversions and ee values, 1.6 equiv of $Zn(OTf)_2$ and 1.2 equiv of *N*-

methylephedrine are required in the general procedure. Furthermore these reaction conditions are still inapplicable to non α or β-branched aldehydes, for example when R_1=4-*t*-butylphenyl and R_2=Et, only 45% yield and 64% ee were achieved.

Considering that Carreira's and related methods are strictly dependent on and limited by the structure of the aldehydes, a catalytic system has been developed which has applicability to a broader array of substrates.

In 2010 the Trost group first published the systematic study of catalytic 1,3-diyne asymmetric addition to aldehydes by using their (*S*,*S*)-ProPhenol ligand **82** (**Figure 60**).[106] Under mild reaction conditions the scope of substrates could be extended to α-branched aliphatic aldehydes and α,β-unsaturated aldehydes without serious erosion of yields or ee values. However there were still some limitations within this system. For example when (Z)-α,β-unsaturated aldehydes were applied, a product of only 63% ee was obtained. Other α-branched aldehydes (up to 83% ee) and aldehydes with a long chain (up to 82% ee) such as octanal are also not ideal substrates for enantioselective diynylation. Furthermore, the use of 2-3 equivalents of the 1,3-diyne is necessary for the full conversion of aldehydes. This protocol has also been applied to total synthesis of (*R*)-strongylodiol A and (*R*)-strongylodiol B and products of 88% ee and 87% ee were obtained respectively. A similar system established by Wang employed a chiral 1,4-amino alcohol as the ligand in place of ProPhenol.[107] This reaction worked very well with aromatic aldehydes but when α,β-unsaturated aldehydes were tested the ee values dropped to 80-84% which is slightly lower than Trost's system. Interestingly, this method also has been applied to the total synthesis of (*R*)-strongylodiol A and (*R*)-strongylodiol B. With aliphatic aldehydes the 1,4-amino alcohol catalyst was less enantioselective; 55% ee for (*R*)-strongylodiol A and 58% ee for (*R*)-strongylodiol B were reported by this method. Although for the first time the ProPhenol/Me_2Zn method makes the 1,3-diyne asymmetric addition a truly catalytic

reaction and extended the scope of aldehyde substrates; the application of this reaction is still strictly restricted by the poor performance in aliphatic aldehyde substrates.

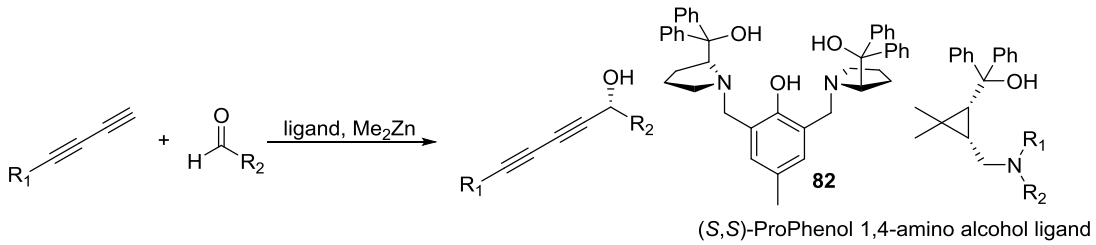


Figure 60. 1,3-Diyne asymmetric addition by Trost's method.

Trost claims the problems they encountered in aliphatic aldehyde 1,3-diyne asymmetric addition were caused by substrate enolization during the course of the reaction.[108] To overcome the challenges in the field of 1,3-diyne asymmetric addition, the 1,1'-binaphth-2-ol (BINOL)/$ZnEt_2$/Ti(O*i*Pr)$_4$ catalytic system developed previously for alkyne addition has been extended to asymmetric 1,3-dialkynes addition by the Pu group (**Figure 61**).[109] This strategy is applicable to aliphatic aldehydes (up to 95% ee), aromatic aldehydes (up to 94% ee) and α,β-unsaturated aldehydes (up to 92% ee). Not only has the substrate scope been extended, the method gives both excellent yields and good selectivities, hence filling the gap left previously.

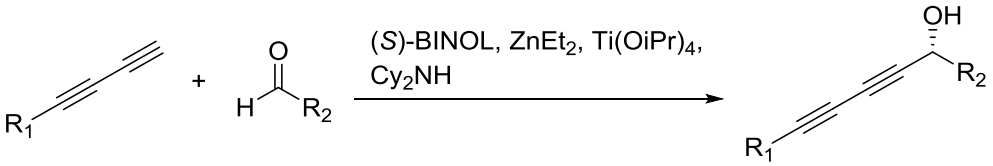


Figure 61. 1,3-Diyne asymmetric addition by Pu's method.

Although the catalytic 1,3-diyne asymmetric addition is an efficient way to access the chiral targets, the application is still limited by the structure of substrates. In general, there are two ways to prepare the 1,3-diynes (**Figure 62**).[109] The synthesis of 1,3-diynes is not efficient and sometimes is even troublesome. Firstly if R is a short chain such as *n*-butyl, the corresponding 1,3-diyne will be too volatile to be separated from benzene or toluene (**Figure 62**, Reaction 1). To date, nobody has published the 1,3-diyne addition using

highly volatile diyne species such as 1,3-octadiyne. Also the preparation of 1,3-diyne is not very economic or environment friendly. To prepare 7 mmol 1,3-diyne it is necessary to consume 380 mL of benzene.[106] Moreover, additional difficulty was caused by the low stability of 1,3-diynes. The publications in this area indicate that 1,3-diynes are unstable at room temperature therefore additional care should be taken when preparing these species.

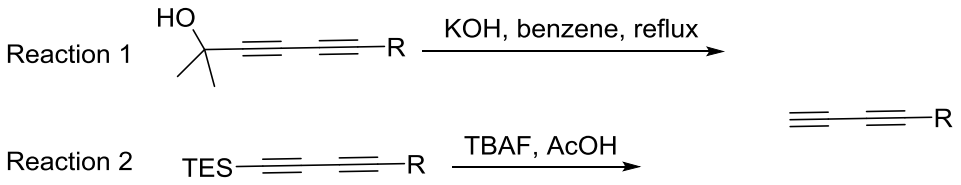


Figure 62. Synthesis of 1,3-diyne.

The use of highly reactive and enolizable aldehydes such as acetaldehyde for 1,3-diyne addition is rare. Only one example of acetaldehyde 1,3-diyne asymmetric addition has been reported (0.2 mmol scale, 66%, 94% ee) by using 4 equivalents of acetaldehyde.[108] Reportedly, when the alkyne addition was performed the acetaldehyde was rapidly consumed by a competing aldol reaction rather than 1,3-dialkyne addition. Although the disfavoured reaction can be partially controlled by tuning the addition speed, the formation of large amounts of side-product is unavoidable.

1.6. The Advantages and Disadvantages of Asymmetric Transfer Hydrogenation Compared to Asymmetric Hydrogenation.

Both asymmetric hydrogenation[193] and asymmetric transfer hydrogenation prochiral unsaturated compounds can be used as one of the most efficient methods to get access of the corresponding chiral products.

With concern to catalyst/substrate diversity, asymmetric hydrogenation apparently has more choices of ligands and metal cores compared to transfer hydrogenation. Thanks to

the diversity the substrate scope of hydrogenation is much broader than transfer hydrogenation.

The substrate scope includes ketones, imines, unfunctionalized alkenes, functionalized alkenes such as α,β-unsaturated esters/acids, enol esters and enamines and heterocycles. The substrate scope of asymmetric transfer hydrogenation is relatively limited because the catalysts are more reactive to electro-deficient double bonds such as ketones, imines, dicyanoolefins and nitroolefins. Furthermore to achieve good enantioselectivities a binding group such as aromatic ring and triple bond conjugations in majority of the case are necessary.

In term of reactivity of catalysts, transfer hydrogenation catalysts are unable to compete with hydrogenation catalysts although during the past twenty years the reactivity has been enormously improved. In a recent publication, Ir catalyzed acetophenone asymmetric hydrogenation can reach 5.0×10^6 S/C loading[194] (91% yield, 98% ee) which is far more active than present transfer hydrogenation method.

The advantages of asymmetric transfer hydrogenation are also very distinctive. First and foremost is the use other hydrogen sources such as isopropanol, HCO_2H and HCO_2Na instead of H_2. Transfer hydrogenation reactions can be carried out at 1 atm pressure therefore simple for operation while high pressure H_2 (30-200 atm for laboratory use) in hydrogenation is unavoidable. Secondly aromatic ring and triple bond are unique binding groups for transfer hydrogenation which is rarely seen in asymmetric hydrogenation.

2. Results and Discussion:

2.1. ATH of 2,2-Dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones and Application to the Total Synthesis of Yashabushitriol.

2.1.1. Synthesis of Ketone Precursors.

Initial studies in this project were directed at the synthesis of 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-one precursors, followed by a study of their asymmetric transfer hydrogenation.

As outlined in **Figure 63**, it was envisaged that the desired ketone precursors could be prepared either from *N*-acylbenzotriazoles or acid chlorides. Literature precedent[110] suggests that direct coupling of an acid chloride is the most convenient and straightforward method to access 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones however some disadvantages, including variable and relatively low yields, may require the use of alternative methods.

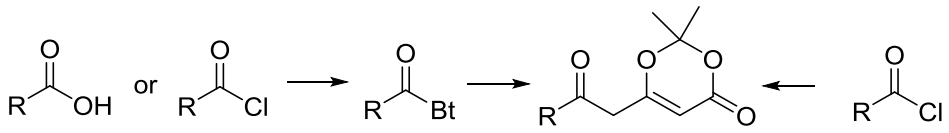


Figure 63. Two possible routes for the synthesis of 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones.

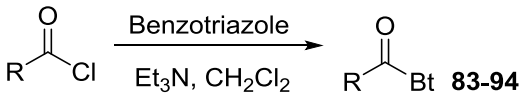
The widely used precursor *N*-acylbenzotriazoles can be easily prepared from carboxylic acids or acid chlorides on large scales (more than 10 g) and in high yields. Literature reported[92] that better yields can be achieved compared to acid chlorides therefore this reaction was enlisted as the secondary plan.

2.1.1.1. Synthesis of *N*-Acylbenzotriazoles.

The synthesis of *N*-acylbenzotriazoles (compounds **83**-**94**) from carboxylic acid chlorides was achieved following El-Dusouqui's method (**Table 1**).[111] High yields (up to 99%) of

products and in generally good purities were achieved after a basic work-up and the products were desiccated to dryness before use without further purification. Katritzky's method[112] of preparing *N*-acylbenzotriazoles (compounds **95-97**) directly from carboxylic acids (**Table 2**) was also adopted for the synthesis of benzotriazole amides when the acid chlorides were not commercially available. By using this method, products were provided in equally high purity as well as high yield despite the requirement for the use of four equivalents of benzotriazole.

Table 1. Synthesis of *N*-acylbenzotriazoles from carboxylic acid chlorides.

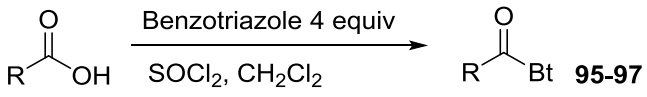


Entry	R (No.)[1]	Yield[2] (%)	Entry	R (No.)[1]	Yield[2] (%)
1	2-Bromophenyl (**83**)	96	6	4-Methoxylphenyl (**88**)	99
2	2-Methylphenyl (**84**)	99	7	3-Methylphenyl (**89**)	99
3	2-Furanyl (**85**)	99	8	Isobutenyl (**90**)	93
4	4-Methylphenyl (**86**)	99	9	Benzyl (**94**)	99
5	4-Fluorophenyl (**87**)	96			

1. Compound number.

2. Isolated yield.

Table 2. Synthesis of *N*-acylbenzotriazoles from carboxylic acids.



Entry	R (No.)[1]	Yield[2] (%)
1	2-Phenylethynyl (**95**)	93
2	2-Thienyl (**96**)	79
3	4-Nitrophenyl (**97**)	81

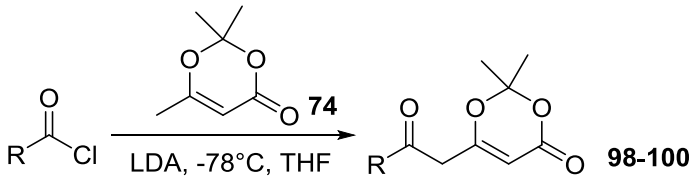
1. Compound number.

2. Isolated yield.

2.1.1.2. Synthesis of 2,2-Dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones.

2,2-Dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones precursors were first synthesized by Katritzky's method.[92] Deprotonation of 2,2,6-trimethyl-1,3-dioxin-4-one **74** by LDA (LDA was prepared in situ) at -78 °C resulted in the formation of the lithium enolate. Claisen condensation occurred after the addition of *N*-acylbenzotriazole/THF solution and the desired ketones were obtained in low to moderate yields (15-46%) (**Table 4**). Attempts to prepare similar ketones from carbonyl acid chlorides (**Table 3**) however led to lower yields compared to the method described in **Table 4**. Since *N*-acylbenzotriazole was completely consumed during the course of the reaction, presumably the poor yields may result from decomposition of products under the basic reaction conditions overnight. Another drawback of this reaction is that a large amount of unreacted 2,2,6-trimethyl-1,3-dioxin-4-one **74** remained in the solution after work-up. Since compound **74** and product have very similar polarity, meticulous column chromatography was needed to separate pure samples from starting material. Furthermore we found that benzotriazole should be completely removed from product. In an attempt to prepare ketone **113** by the method described in **Table 4**, benzotriazole could not be completely removed even after column chromatography twice. When treating the impure sample under standard transfer hydrogenation conditions no reaction was observed. Considering the coordination ability of benzotriazole it is likely that benzotriazole acting as a catalyst inhibitor.

Table 3. Synthesis of 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones from carboxylic acid chlorides.

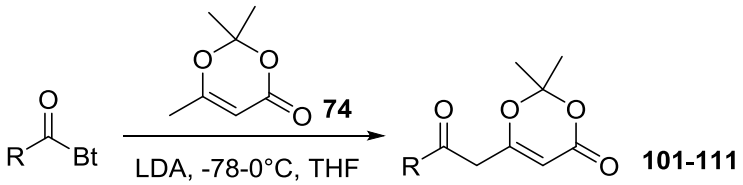


Entry	R(No.)[1]	Yield[2] (%)
1	Methyl (**98**)	15
2	Phenyl (**99**)	26
3	*trans*-Cinnamonyl (**100**)	13

1. Compound number.

2. Isolated yield.

Table 4. Synthesis of 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones from *N*-acylbenzotriazoles.



R(No.)[1]	Yield[2] (%)	R(No.)[1]	Yield[2] (%)
2-Bromophenyl (**101**)	21	4-Nitrophenyl (**107**)	36
2-Methylphenyl (**102**)	30	Isobutenyl (**108**)	28
2-Furanyl (**103**)	27	2-Phenylethynyl (**109**)	15
4-Methylphenyl (**104**)	46	3-Methylphenyl (**110**)	46
4-Fluorophenyl (**105**)	38	Benzyl (**111**)	15
4-Methoxylphenyl (**106**)	39		

1. Compound number.

2. Isolated yield.

2.1.1.3. Second Generation Synthesis of 2,2-Dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones.

To counteract the inefficiency found in the previous synthesis a new synthetic pathway was designed (**Figure 64**). In this approach, *N*-acylbenzotriazoles were replaced by aldehydes, which have proved to be better nucleophilic acceptors for the 2,2,6-trimethyl-1,3-dioxin-4-one lithium enolate. The reaction was carried out under the conditions shown in **Table 5** and alcohols (compounds **114**-**123**) were found to be the only products after work-up. The products were readily separated from starting materials in improved yields (up to 97%). In addition, products of this step could also be used subsequently as racemic standards for HPLC.

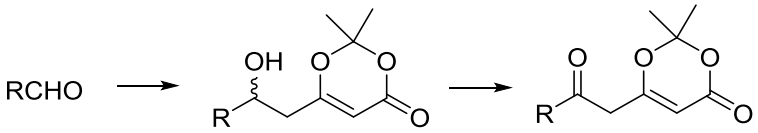


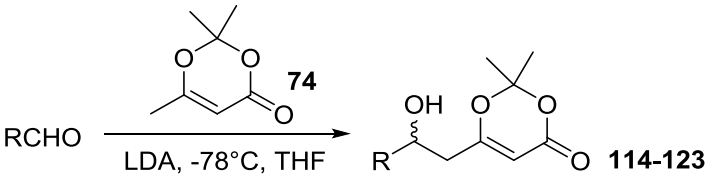
Figure 64. An alternative routes for the synthesis of 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones.

In the second step, the alcohols were oxidized by PCC in CH_2Cl_2 at room temperature. The PCC oxidation was finished in a few hours and in general no dehydration product or over-oxidation of the double bond was detected. Taking advantage of this clean reaction, the ketones in **Table 6** could be separated easily (on a large scale, 7 g of ketone **99** was prepared) with purity that is good enough for a S/C 5000/1 reduction (see ATH part). Although the PCC oxidation can offer clean products effectively, the method is not compatible with certain R groups including *trans*-cinnamonyl and 2-furanyl (**Table 6, Entries 10** and **11**). PCC will inevitably oxidize the furan ring and may break the double bond of the *trans*-cinnamonyl group. Other oxidative systems such as pyridine-sulphur trioxide (SO_3·Py)/base and Swern oxidation all failed in this transformation (**Figure 65**). When those two reactions were performed, only the dehydration product was found. Dess-

Martin oxidation of this compound has been published by Lee;[113] but considering the cost of the Dess-Martin reagent, PCC oxidation is more economic, equally efficient and achieves a sufficiently clean transformation.

The second generation procedure was able to furnish the ketones on a multi-gram scale and with enough purity to pave the way for the asymmetric transfer hydrogenation and a target related synthesis.

Table 5. Synthesis of racemic samples by Claisen-type condensation.[1]



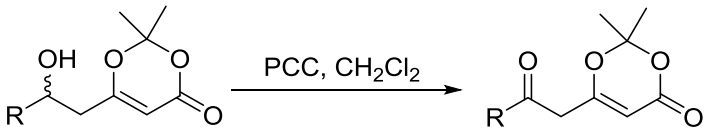
R(No.)[2]	Yield[3] (%)	R(No.)[2]	Yield[3] (%)
Phenyl (**114**)	66	2-Thienyl (**119**)	58
4-Nitrophenyl (**115**)	66	2-Methylphenyl (**120**)	84
4-Methylphenyl (**116**)	60	4-Fluorophenyl (**121**)	81
3-Methylphenyl (**117**)	81	4-Methyoxyphenyl (**122**)	77
4-Bromophenyl (**118**)	60	2-Furyl (**123**)	97

1. Aldehydes were used directly without distillation.

2. Compound number.

3. Isolated yield.

Table 6. Synthesis of 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones by PCC oxidation.



Entry	R(No.)[1]	Yield[2] (%)	Entry	R(No.)[1]	Yield[2] (%)
1	Phenyl (**99**)	89	6	2-Thienyl (**113**)	76
2	4-Nitrophenyl (**107**)	46	7	2-Methylphenyl (**102**)	67
3	4-Methylphenyl (**104**)	73	8	4-Fluorophenyl (**105**)	64
4	3-Methylphenyl (**110**)	81	9	4-Methyoxyphenyl (**106**)	93
5	4-Bromophenyl (**112**)	80	10	*trans*-Cinnamonyl (**100**)	0
			11	2-Furyl (**103**)	0

1. Compound number.

2. Isolated yield.

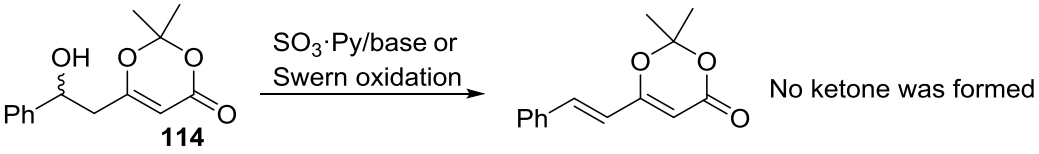


Figure 65. Failed oxidations under other conditions.

2.1.2 Asymmetric Transfer Hydrogenation of 2,2-Dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones.

2.1.2.1. Optimization of Reaction Conditions.

The asymmetric transfer hydrogenation of 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones commenced from the optimization of reaction conditions by using 2,2-dimethyl-6-(2-oxo-2-phenylethyl)-4H-1,3-dioxin-4-one **99** as starting material. This compound proved to be stable when treated in HCO_2H/TEA 5/2 mixture at rt for a week. At elevated temperature (40°C and 50°C) the compound is stable for up to 3 days although literature

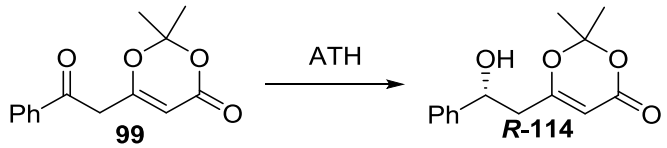
reports indicate that dioxin-4-one ring can be cleaved at high temperature through a retro-Diels-Alder reaction.[92]

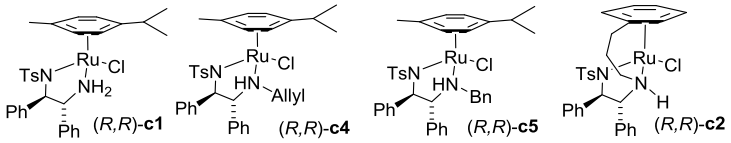
From solvent screening tests (**Table 7**, Entries 1-5) it was found that the catalyst reactivity is highly solvent dependent. HCO_2H/TEA 5/2 mixture, EtOAc and THF are not suitable solvents for this reduction presumably because of the strong interaction between solvent and ketone substrate. When CH_2Cl_2 and CH_3CN were tested as solvents the reaction rates were substantially increased. In the ATH of acetophenone **13**, when HCO_2H/TEA were used as a hydride donor the reaction efficiency was only slightly affected by the choice of solvent. But in the case of compound **99**, the reduction rate is highly solvent dependent.

Subsequently, the reactivities of catalysts were tested. As expected, the tethered catalyst (*R*,*R*)-**c2** yields the best results against catalysts (*R*,*R*)-**c1**, (*R*,*R*)-**c4** and (*R*,*R*)-**c5**; it could fully convert compound **99** within 7 h at rt with 1 mol% catalyst loading. The reactivity of catalyst (*R*,*R*)-**c1** is lower although 2 mol% of is enough to reach full conversion of the compound **99** within 24 h. The lowest catalytic reactivities were observed using catalysts (*R*,*R*)-**c4** and (*R*,*R*)-**c5** in which the N of the ligands had been modified with allyl or Bn. In fact, *N*-substituted catalysts (**Table** 7, Entries 6 and 7) hardly convert any substrate under exactly the same conditions.

Tethered catalyst (*R*,*R*)-**c2** of varied loading and different reaction temperatures were investigated. As demonstrated in **Table 7** Entries 8-12, one molecule of (*R*,*R*)-**c2** could reduce up to 1000 molecules of **99** at rt. More interestingly when the same reaction were tested at 40°C and 50°C, although the reactions were more rapid, the enantioselectivities were maintained at the same level (**Table** 7, Entries 11 and 12). When (*R*,*R*) configuration catalyst was used the absolute configuration of **114** was unambiguously assigned to be *R* by comparing the optical rotation with that reported.[88]

Table 7. Optimization of reaction conditions.





Entry	Catalyst	Solvent[1,2]	S/C	T (°C)	Time (h)	Conv (%)[3]	ee (%)[4]
1	(*R*,*R*)-**c1**	HCO_2H/TEA 5/2	50/1	rt	80	<10	-
2	(*R*,*R*)-**c1**	EtOAc	50/1	rt	80	33	98 (*R*)
3	(*R*,*R*)-**c1**	THF	50/1	rt	80	63	98 (*R*)
4	(*R*,*R*)-**c1**	CH_2Cl_2	50/1	rt	13	100	98 (*R*)
5	(*R*,*R*)-**c1**	CH_3CN	50/1	rt	13	100	98 (*R*)
6	(*R*,*R*)-**c4**	CH_2Cl_2	50/1	rt	24	<10	-
7	(*R*,*R*)-**c5**	CH_2Cl_2	50/1	rt	24	<10	-
8	(*R*,*R*)-**c2**	CH_2Cl_2	100/1	rt	7	100	98 (*R*)
9	(*R*,*R*)-**c2**	CH_2Cl_2	500/1	rt	29	100	98 (*R*)
10	(*R*,*R*)-**c2**	CH_2Cl_2	1000/1	rt	70	>99	98 (*R*)
11	(*R*,*R*)-**c2**	CH_2Cl_2	1000/1	40	17	100	98 (*R*)
12	(*R*,*R*)-**c2**	CH_2Cl_2	1000/1	50	10	100	98 (*R*)

1. Substrate concentration is 0.15 M.

2. 5 Equivalent of formic acid were used when organic solvents were used.

3. Conversions were determined by ^{1}H NMR.

4. Ee values were determined by chiral HPLC, CHIRALPAK IB column.

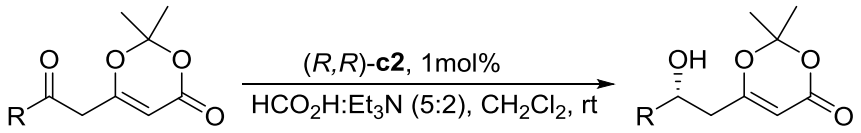
2.1.2.2. ATH of 2,2-Dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones at rt.

Under optimized conditions catalyst (*R*,*R*)-**c2** was tested at room temperature with a selection of substrates bearing different R groups. We found the reaction time is substituent dependent; when R=alkyl, alkenyl, alkynyl and aryl without strong electron-donating groups or atoms the reactions finished within 24 h; on the contrary

if a strong electron-donating group or atom was attached to aryl the reactivities of the substrates were decreased (**Table 8**, Entries 12 and 13). The enantioselectivities however appear to have no relevance to reaction time. The relationship between ee values and R groups is also very clear. When R=phenyl or substituted phenyl all the ee values that were obtained were excellent except for 2-bromophenyl (**Table 8**, Entry 11), which may be due to the electronic/steric effect causing disruption of the interaction between the catalyst and the aromatic ring of the substrate.

As expected, when R=phenylacetylenyl (Entry 2) the reaction proceeded with an excellent ee value (98% ee) while ee values were eroded for R=*trans*-Cinnamonyl (73% ee) (Entry 8) and isobutenyl (70% ee) (Entry 14). The poorest ee (59% ee) was for R=methyl (Entry 15) which suggested that methyl is not a good group for asymmetric induction. By comparing the optical rotation of compound **128** with the literature value[114] the absolute configuration was determined to be (*S*) which was still consistent with other compounds.

Table 8. ATH of 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones at rt.



Entry	Product[1](No.)[2]	Time (h)[3]	Yield (%)[4]	ee (%)[5]
1	Phenyl (*R*-**114**)	7	89	98
2	Phenylacetylenyl (*R*-**124**)	8	82	98
3	4-Nitrophenyl (*R*-**115**)	8	94	96
4	4-Methylphenyl (*R*-**116**)	12	96	97
5	3-Methylphenyl (*R*-**117**)	12	98	98
6	4-Bromophenyl (*R*-**118**)	15	87	98
7	2-Thienyl (*R*-**119**)	24	95	98
8	*trans*-Cinnamonyl (*R*-**125**)	25	99	73
9	2-Methylphenyl (*R*-**120**)	30	90	98
10	4-Fluorophenyl (*R*-**121**)	30	98	99
11	2-Bromophenyl (*R*-**126**)	40	88	82
12	2-Furyl (*R*-**123**)	50	91	99
13	4-Methoxylphenyl (*R*-**122**)	180	92	98
14	Isobutenyl (*R*-**127**)	8	18	70
15	Methyl (*S*-**128**)	16	89	59

1. Absolute configurations of known compounds were determined by optical rotation and unknown compounds were assigned by analogy.

2. Compound number.

3. Reaction time was determined by following the reaction by TLC.

4. Isolated yield.

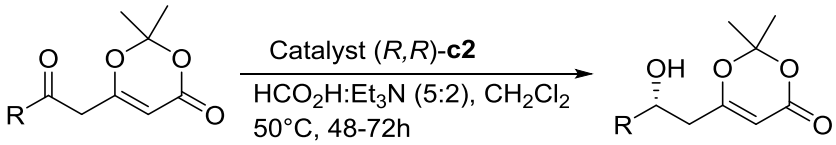
5. Ee values were determined by chiral HPLC, CHIRALPAK IB column.

2.1.2.3. ATH of 2,2-Dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones at Elevated Temperature.

Ketones prepared from the PCC oxidation were reduced at 50 °C by using catalyst (*R*,*R*)-**c2** (**Table 9**). It is necessary for the reactions to be completed within 72 h because of the relatively low thermal stability of the 1,3-dioxin-4-one ring. As shown in **Table 9**, under

these conditions, with the exception of the results shown in **Table 9** Entries 7 and 10, all the substrates were reduced at a 0.1 mol% catalyst loading. In Entry 2, when R=phenyl, 0.02 mol% of catalyst was used and the reaction was still completed within 72 h. Alcohol *R*-**114** was obtained with excellent enantioselectivity (98% ee) without significant decomposition although the yield is slightly lower than Entry 1.

Table 9. ATH of 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones at elevated temperature.



Entry	R(No.)[1]	S/C	Yield[2] (%)	ee[3] (%)
1	Phenyl (*R*-**114**)	1000/1	98	98
2	Phenyl (*R*-**114**)	5000/1	93	98
3	4-Nitrophenyl (*R*-**115**)	1000/1	82	95
4	4-Methylphenyl (*R*-**116**)	1000/1	92	98
5	3-Methylphenyl (*R*-**117**)	1000/1	91	98
6	4-Bromophenyl (*R*-**118**)	1000/1	95	97
7	2-Thienyl (*R*-**119**)	500/1	98	99
8	2-Methylphenyl (*R*-**120**)	1000/1	94	>95
9	4-Fluorophenyl (*R*-**121**)	1000/1	85	98
10	4-Methyoxyphenyl (*R*-**122**)	500/1	76	98

1. Compound number.

2. Isolated yield.

3. Ee values were determined by chiral HPLC, CHIRALPAK IB column.

The concise synthesis of this type of compounds could facilitate the total synthesis of compounds bearing a chiral hydroxyl at the benzyl position such as yashabushitriol,[115] (*R*)-(+)-kavain[116] and (-)-centrolobine.[117]

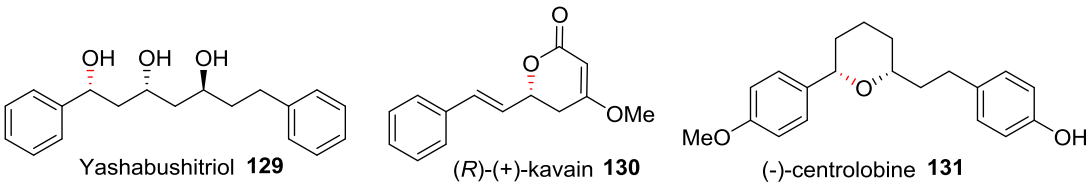


Figure 66. Potential targets.

2.1.3. Total Synthesis of Yashabushitriol.

Yashabushitriol **129** was isolated from the male flowers of *Alnus sieboldiana* (252 mg from 9.2 kg male flowers) and bears a 1,3,5-triol structure.[115] The absolute configuration of this compound has been determined to be (1*R*), (3*R*), (5*S*) based on the reduction of the known yashabushiketodiol and ^{1}H NOE analysis. To date, only one racemic synthesis[118] and one formal synthesis[119] of compound **129** have been published. Because of the lack of full data for compound **129** as well as the attractive synthetic strategy (which includes two highly stereo-selective ATH and one chemo-selective hydrogenation), an asymmetric synthesis of yashabushitriol **129** was developed by using the method described in **Figure 67**.

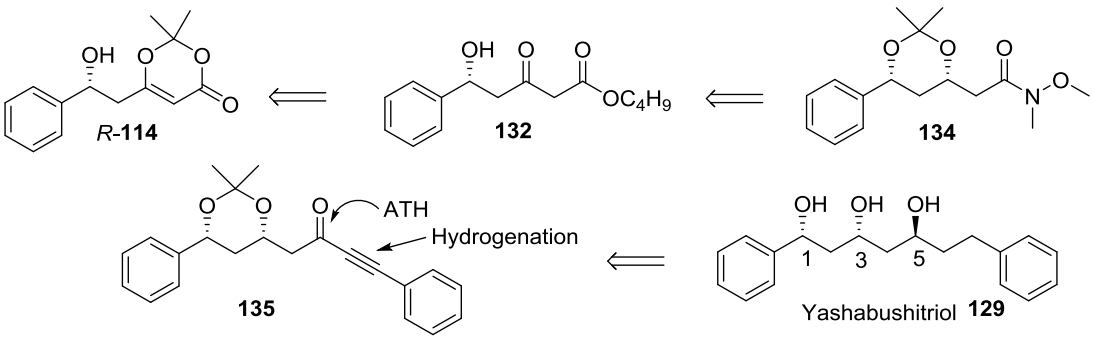
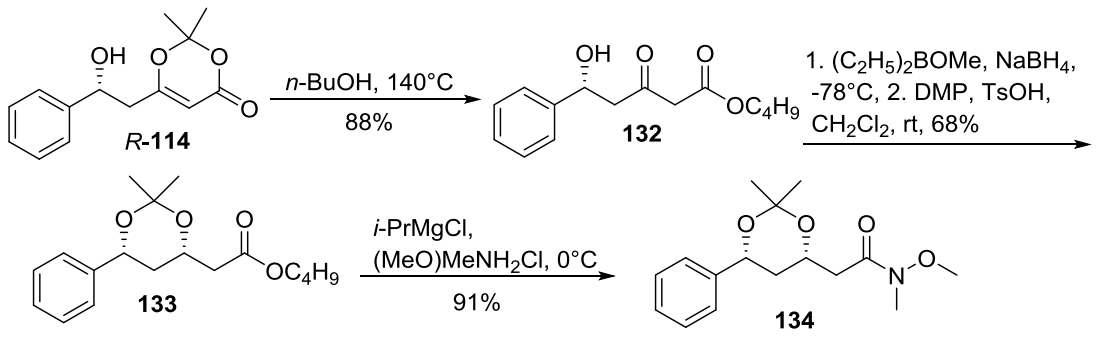


Figure 67. Synthesis plan of yashabushitriol **129**.

As the C1 hydroxyl group is in the vicinal position of phenyl, it was envisaged that the C1 hydroxyl could be installed through the ATH of the corresponding ketone **99** which was prepared on a 7 g scale and in 98% ee. The chiral C3 hydroxyl group could be introduced through a chelation controlled *cis* selective reduction after conversion to a,β-keto ester **132**,

then by two more steps to reach the Weinreb amide **134**. After conversion to a propargylic ketone **135** from **134**, ATH provides a convenient way to introduce the C5 asymmetry. Finally the triple bond should be hydrogenated and acetonide removed to complete the synthesis of yashabushitriol **129**. Other steps required for the synthesis include Weinreb amide formation, acetonide protection and deprotection, all of which are well established transformations.

The synthesis (**Scheme 1**) commenced from the enantiomerically enriched alcohol *R*-**114** which is available through the reduction described above. The 1,3-dioxin-4-one ring-opening reaction proved to be a convenient way to form the required β-keto ester. Under the *n*-butanol reflux conditions, this was converted in high yield to a single product **132.** The resulting β-keto ester **132** was reduced *cis* selectively by applying Snider's procedure[120] ($(C_2H_5)_2BOMe/NaBH_4$) and the resulting crude 1,3-diol was protected by formation of an acetonide. After protection, the diastereoselectivity of the crude mixture was determined to be *syn*/*anti*=5/1 by ^1H NMR. The well established highly *syn*-selective reduction[121] did not work very well for compound **132**. The Meshram group[122] employed $Zn(BH_4)_2$ in the reduction of a similar compound and using this method the diastereoselectivity could reach *syn*/*anti*=10/1.



Scheme 1. Synthesis toWeinreb amide **134.**

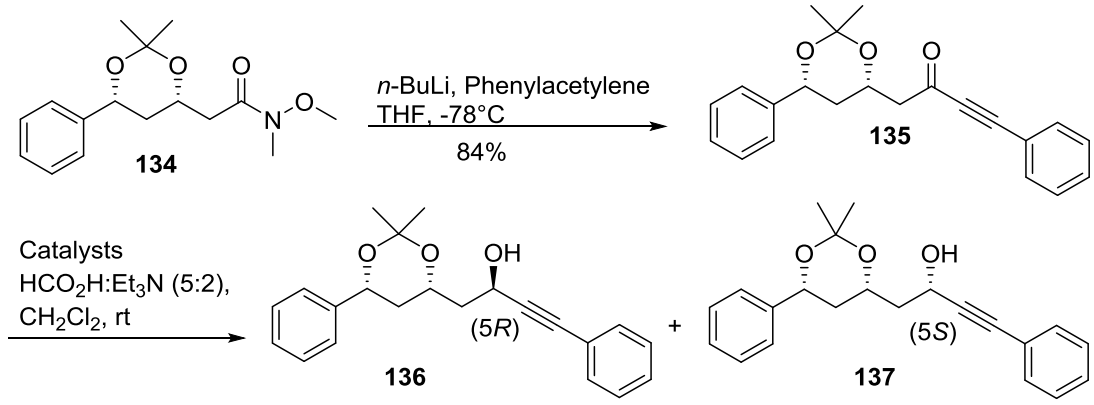
The major *syn* product **133** could be easily separated from the *anti* diastereomer by silica gel column chromatography. Literature precedent suggests that the *syn* conformation is a

chair while the *anti* product is a twisted boat. The difference between them can easily be determined by Rychnovsky ^{13}C NMR analysis.[123] From the ^{13}C NMR of compound **133**, the relative configuration was unambiguously assigned to be *syn*.

At this stage, we were aware that ester **133** would not be a good electrophile for phenylacetylene coupling. To address this, a standard Grignard reagent promoted Weinreb amide formation[124] was used to form compound **134** which was employed for the subsequent coupling step.

As anticipated, the coupling reaction preceded well (**Scheme 2**) and the propargylic ketone **135** was isolated in 84% yield without side-products being observed. The ketone was reduced to alcohol **136** using 1 mol% (*R*,*R*)-**c2** with excellent dr selectivity (5*R*/5*S*=37/1) and yield (94%). The diastereoselectivity of the reduction was fully investigated by using catalysts of different structures and different absolute configurations. When the racemic catalyst ±**c3** was used (**Table 10**, Entry 6), the poor dr value (5*R*/5*S*=1/1.6) suggested the 5*S* product **137** was slightly favoured by the induction of intrinsic chirality of the acetonide ring. The 1/1.6 ratio of diastereoisomers also suggests that the effect of substrate control is not significant. When the chiral catalysts **c1** and **c2** were employed, the chirality was controlled by the communal directing effects of both the substrate and the catalysts. When (*S*,*S*) catalysts were applied both catalysts and substrate preferentially direct the C-5 hydroxyl toward the (*S*) configuration. Therefore in a "matched" case, both (*S*,*S*)-**c1** and (*S*,*S*)-**c2** catalysts provided excellent dr values. When (*R*,*R*) catalysts were applied the situation was reversed; (*R*,*R*) catalysts tend to form (*R*) configuration products whilst the substrate directs the C-5 hydroxyl towards the (*S*) configuration. In this situation, it is expected that the catalyst control could outweigh substrate control; so the desired (*R*) configuration could still be formed. Nearly total catalyst control was found in the case of the (*R*,*R*)-**c2** catalyst reduction (**Table 10**, Entries

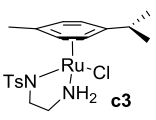
1 and 2). As anticipated, the resulting alcohol has both a very high diastereoselectivity (dr=37/1) and the correct configuration (5*R*) although it is formed through a "mismatched" transition state. This total catalyst control suggests that the physical interaction between the (*R*,*R*)-**c2** catalyst and the chirality of the acetonide ring is not high enough to jeopardize or slow down the favoured transition state formation. What is unexpected is that the substrate-catalyst mismatch was slightly intensified by using (*R*,*R*)-**c1** catalyst; the relatively poor diastereoselectivity (dr=10/1 but still in favour of 5*R*) indicated that the favoured transition state was partially hindered by the substrate (**Table 10**, Entry 3).



Scheme 2. Synthesis and ATH of compound **135** by using different catalysts.

Table 10. Results for ATH of compound **135**.

Entry	Catalyst	Loading (mol %)	dr[1] (5*R*/5*S*)	Yield[2] (%)
1	(*R*,*R*)-**c2**	1	37/1	94
2	(*R*,*R*)-**c2**	5	37/1	93
3	(*R*,*R*)-**c1**	5	10/1	99
4	(*S*,*S*)-**c2**	5	1/30	99
5	(*S*,*S*)-**c1**	5	1/29	99
6	**±c3**[3]	5	1/1.6	73

1. Dr values were determined by ^{1}H NMR.
2. Isolated yield.
3. Structure of ±**c3** catalyst 

c3

With sufficient **136** in hand, the synthesis continued with a late stage triple bond reduction and deprotection. Compound **136** was subjected to a hydrogenation which is seemingly simple but proved to be problematic. A catalytic amount of $Pd(OH)_2/C$ (Pd 20% w/w) was used initially to reduce the triple bond. The reaction was completed within 30 min under 1 atm H_2; however by analyzing the crude ^1H NMR it was found that the H_1 that should be present at 4.9 ppm was missing (**Figure 68**). Concomitant with H_1, peaks which belong to the acetonide (two singlets at 1.70-1.50 ppm) were also not present. From TLC apart from one spot that was close to the place of starting material (protected yashabushitriol), another more polar spot (which is not yashabushitriol) was found. After separation and ^1H NMR analysis the major product was shown to not be yashabushitriol **129** but (-)-yashabushidiol B (protected yashabushitriol/(-)-yashabushidiol B =1/5). This may be because $Pd(OH)_2/C$ is too active and can remove the OH at the benzylic position. Therefore a milder catalyst Pd/C(en) (Pd 20% w/w) was applied to this reaction. Literature precedents[125] suggested that Pd/C(en) (in which Pd/C is poisoned by ethylenediamine) is unable to remove a benzyloxy group. Unfortunately hydrogenolysed product (-)-yashabushidiol B was still found in the reaction mixture when using this catalyst; probably due to incomplete poisoning. Another problem of Pd/C(en) catalyst is that the catalytic activity dropped substantially which makes it difficult to control the reaction time. After 18 h the starting material was still incompletely consumed using 5% of catalyst.

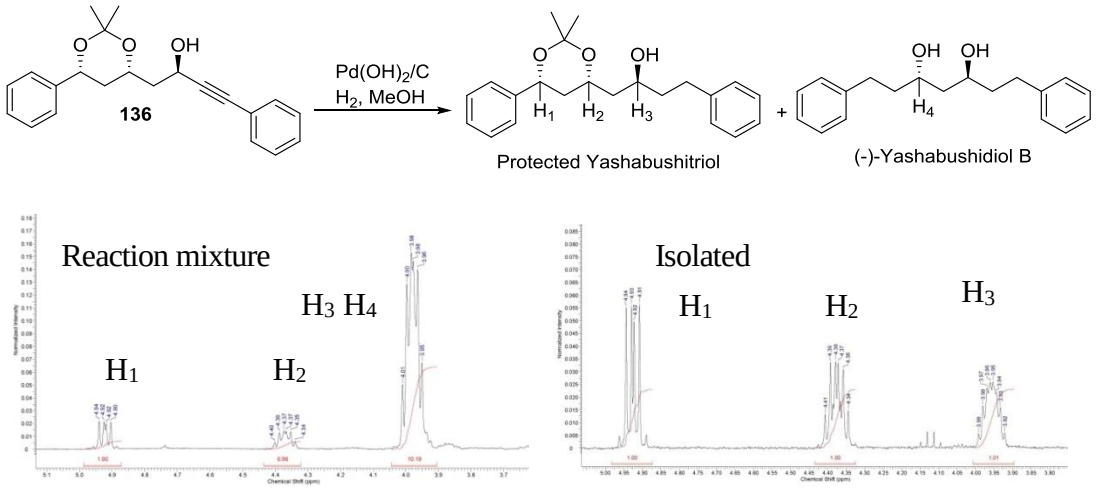
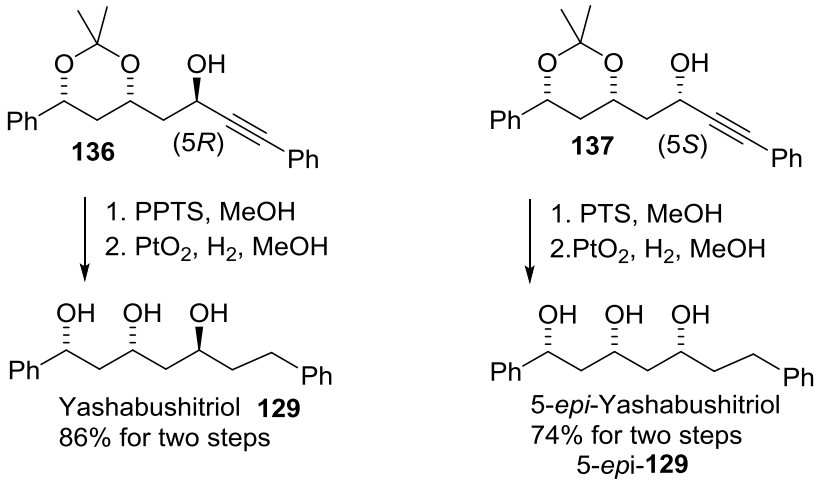


Figure 68. Hydrogenolysis (over reduction) in Pd catalysed hydrogenation.

A slower hydrogenation may result in the formation of more yashabushidiol B, hence Pd/C(en) is also not the ideal hydrogenation catalyst for this reaction. To overcome this aforementioned over reduction, PtO_2 was chosen to minimize hydrogenolysis. Taking into account the fact that acetonide is an electron-withdrawing group which will facilitate hydrogenolysis, it should be removed first. Acetonide protection was removed using PPTS and the crude product was used directly after passing through a short silica gel column. Using a catalytic amount of PtO_2 (6-7 mol%), the carbon-carbon triple bond was reduced smoothly within 30 min under 1 atm hydrogen gas atmosphere whilst the benzyl hydroxyl remained intact (**Scheme 3**). The final product, yashabushitriol **129**, was generated as the only product after hydrogenation in excellent yield (86% over two steps). According to the same principle, the 5*S* isomer was also used in the hydrogenation and 5-*epi*-yashabushitriol 5-*epi*-**129** was obtained with satisfactory yield (74 % over two steps). The absolute structure of synthetic yashabushitriol **129** was confirmed unambiguously by X-ray crystallography (**Figure 69**). The absolute structure of yashabushitriol also served to prove that the absolute structure of the natural **129** has been assigned correctly in previous publications. Unfortunately 5-*epi*-Yashabushitriol is an amorphous solid therefore the

absolute 5-*epi* configuration was assigned as (*S*) by comparing chemical shifts with yashabushitriol and empirical knowledge of the enantioselectivity of ATH reactions.



Scheme 3. Completion of the synthesis of yashabushitriol and 5-*epi*-yashabushitriol.

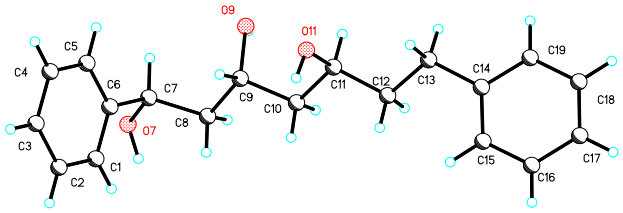
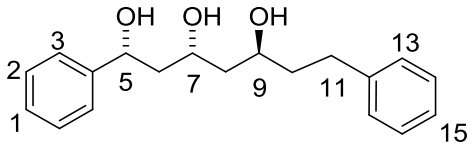


Figure 69. X-Ray crystallography of yashabushitriol.

The NMR data, the melting point and optical rotation values of synthetic yashabushitriol also match the authentic natural sample. Considering it is the first asymmetric total synthesis of yashabushitriol and 5-*epi*-yashabushitriol and the original NMR data of this compound was not fully reported it is useful to compare the ^{1}H and ^{13}C NMR data of these two compounds with the natural one (**Table 11**).

Table11. [1]H and [13]C NMR assignment of natural yashabushitriol, synthetic yashabushitriol and 5-*epi*-yashabushitriol.



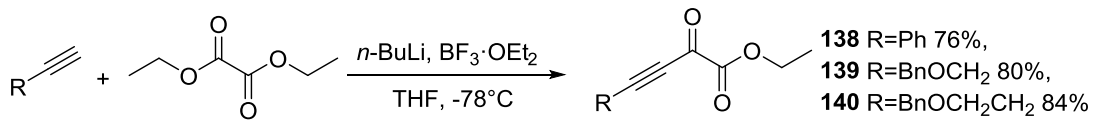
H	Natural yashabushitriol	Synthetic yashabushitriol	5-*epi*-yashabushitriol	C	Natural yashabushitriol	Synthetic yashabushitriol	5-*epi*-yashabushitriol
H1	-	7.38-7.15	7.37-7.15	C1	-	127.7	127.7
H2	-	7.38-7.15	7.37-7.15	C2	-	128.6	128.6
H3	-	7.38-7.15	7.37-7.15	C3	-	128.4	128.4
H5	4.92	4.98	4.94	C4	144.3	144.3	144.3
H6	-	2.02, 1.73-1.67	1.95-1.52	C5	74.6	75.4	75.3
H7	4.30	4.38-4.31	4.20	C6	45.2	45.1	46.0
H8	-	1.73-1.67	1.95-1.52	C7	69.6	70.4	73.5
H9	3.96	4.04-3.96	3.96-3.88	C8	43.1	42.8	43.5
H10	-	1.93-1.83, 1.81-1.78	1.95-1.52	C9	68.1	68.6	72.2
H11	-	2.80, 2.66	2.79-2.59	C10	39.1	39.2	39.7
H13	-	7.38-7.15	7.37-7.15	C11	32.0	32.1	31.7
H14	-	7.38-7.15	7.37-7.15	C12	142.0	142.0	141.9
H15	-	7.38-7.15	7.37-7.15	C13	-	125.7	125.7
				C14	-	128.5	128.5
				C15	-	126.9	125.9

[1, 13]C (125 MHz) and [1]H NMR (500 MHz) spectroscopic data for natural yashabushitriol in $CDCl_3$. [13]C (100 MHz) and [1]H NMR (400 MHz) spectroscopic data for synthetic yashabushitriol and 5-*epi*-yashabushitriol in $CDCl_3$.

2.2 Asymmetric Transfer Hydrogenation of Functionalized Propargylic Ketones.

2.2.1. Synthesis of Propargylic α-Keto Esters and Their ATH Study.

Three propargylic α-keto esters (**138-140**) were prepared by following the procedure above (**Scheme 4**). But when they were treated with HCO_2H/TEA(5:2)/CH_2Cl_2 (TEA 0.3 M) solution it was found that the compounds were unstable. Assuming that propargylic α-keto esters are unstable under basic conditions another stability test was performed in HCO_2Na (1 M) in DMF/H_2O 1:1 solution. All of the three α-keto esters completely decomposed within 3 h at rt which further confirmed that propargylic α-keto esters are sensitive to base. Fortunately compound **138** is relatively stable in HCO_2H/TEA(5:2)/CH_2Cl_2 (TEA 0.3 M) solution but when 10 mol% of catalyst (*R*,*R*)-**c1** was added there was no reduction at all.

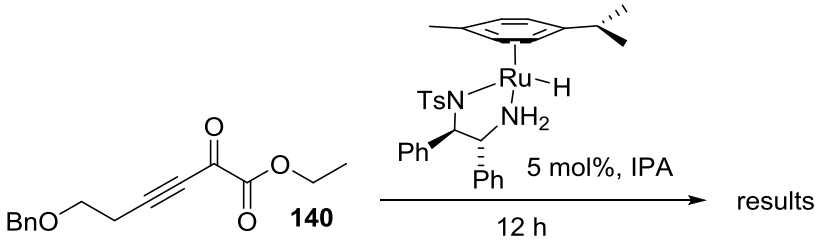


Scheme 4. Synthesis of propargylic α-keto esters.

Further ATH studies were carried out in isopropanol and with activated catalyst (*R*,*R*)-**c1**; the conditions chosen have been proven to be base free. Compound **140** was chosen for the ATH tests in isopropanol. Three reactions were carried out independently under the same conditions. When only freshly prepared ketone **140** was used there was no reduction at all (**Table 12**, Entry 1). In the test of mixed material reduction neither ketone **140** nor acetophenone could be reduced (**Table 12**, Entry 2). To make sure that the reaction conditions and the activated catalyst was working for other ketones, only acetophenone was used as starting material. Without **140**, acetophenone was completely reduced overnight (**Table 12**, Entry 3). This experimental result suggests that the activated catalyst is no longer active in the presence of ketone **140**. Looking back the structure of the

propargylic α-keto ester, both ketone and ester act as electron-withdrawing groups thus making propargylic α-keto ester a very active Michael addition acceptor which could potentially inhibit catalyst (*R*,*R*)-**c1** by reacting with amine ligand. The stability issue may also be a result of the electron-withdrawing ability of α-keto esters such that the triple bond could be attacked by OH^- or some other nucleophiles in HCO_2Na/H_2O solution. Although all the attempts at reducing propargylic α-keto esters failed, the unique property of this class of compounds may serve as an example that helps to establish the general rules for ATH of propargylic ketones.

Table 12. ATH study of compound **140**.



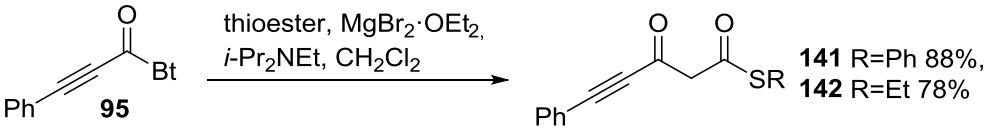
Entry	Starting material	Result
1	pure compound **140**	no reduction
2	**140** and acetophenone 1/1 mixture	no reduction
3	pure acetophenone	complete reduction

2.2.2. Synthesis of Thioesters, Acid Monoesters, Acid Chloride Monoesters and Weinreb Diamides.

The synthesis of thioesters (**157-159**), acid monoesters (**147-150**), acid chloride monoesters (**151-154**) and Weinreb diamides (**155** and **156**) were achieved following by literature procedures. Since these are known compounds and some are commercially available the full preparation will not be discussed. The preparation and references are listed in the experimental section.

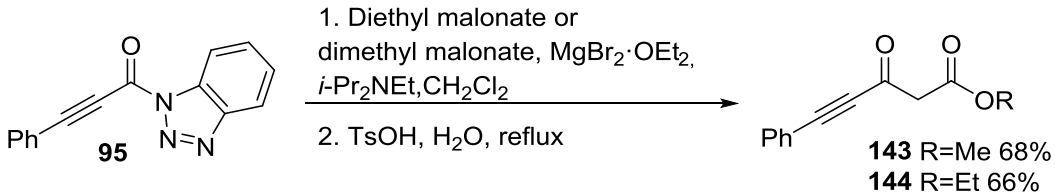
2.2.3. Synthesis of Propargylic β-Keto Thioesters, Propargylic β-Keto Esters and Propargylic α-Methyl-β-keto Esters and Their ATH Study.

Two propargylic β-keto thioesters (**141** and **142**) were prepared by a direct Claisen type reaction triggered by the soft enolization of thioesters (**Scheme 5**).[126] Under these mild reaction conditions self-Claisen condensation of thioesters and other side reactions were prevented. Good yields were achieved when both phenyl thioacetate and ethyl thioacetate were used as substrates. The products were pure enough from ^{1}H NMR analysis for direct use in asymmetric transfer hydrogenation studies.



Scheme 5. Synthesis of propargylic β-keto thioesters.

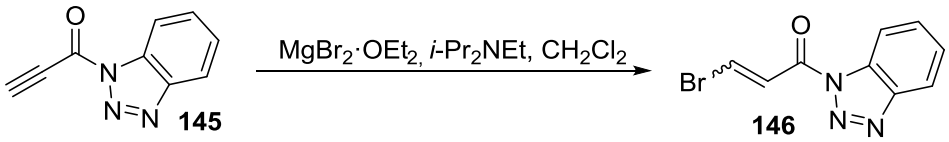
Unlike ethyl thioacetate, ethyl acetate is inapplicable to these soft enolization conditions due to its relatively high pKa value. An alternative route was developed by using diethyl malonate and dimethyl malonate as nucleophilic reagents, both of which readily enolized under $MgBr_2 \cdot OEt_2$/*i*-Pr_2NEt conditions. The reactions happened smoothly when malonate nucleophiles were used; after work-up the Bt-H was removed using a silica gel column and the condensation products were refluxed in TsOH (0.3 % w/w)/water until the diesters were completely consumed.[127] The two propargylic β-keto esters (**143** and **144**) were isolated in good yields (**Scheme 6**).



Scheme 6. Synthesis of propargylic β-keto esters (**143** and **144**) by Claisen condensation.

Not all the propargylic β-keto esters could be prepared by the reaction illustrated in **Scheme 6**. The following example in **Scheme 7** demonstrates that if the other side of

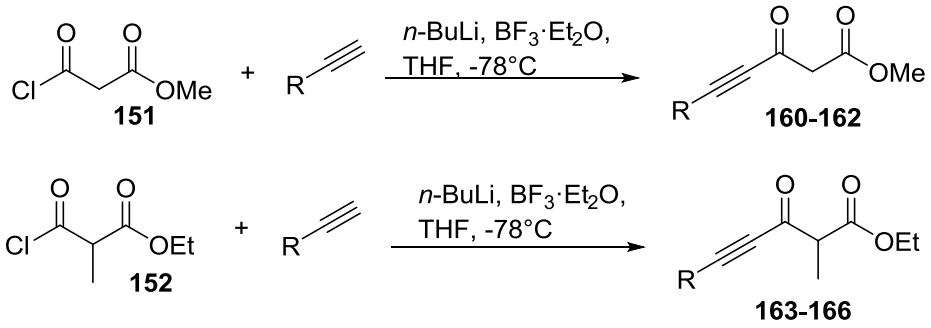
propargylic benzotriazoleamide is H then a Michael addition will happen easily between the starting material and $MgBr_2 \cdot OEt_2$. Hence the soft enolization reaction is conditional, and cannot be applied to all the propargylic benzotriazole amide substrates. Additionally, propargylic benzotriazole amides prepared from propargylic carboxylic acids are not always commercially available, which limits the scope of the methodology.



Scheme 7. A typical side-reaction.

The synthesis of propargylic β-keto esters and propargylic α-methyl-β-keto esters was achieved following Yamaguchi's conditions[128] using chlorides (**151** and **152**) and *in situ*-generated alkynyl boranes. Compared to lithium acetylide, the less reactive alkynyl borane species only react with carbonyl chlorides therefore side reactions are minimized. From the experimental results, the synthesis of α-methyl-β-keto esters proceeded in generally higher yields than the propargylic β-keto esters (**Table 13**).

Table 13. Synthesis of propargylic β-keto esters and propargylic α-methyl-β-keto esters.



Entry	R	β-Keto esters Yield[1] (%)(No.)[2]	α-Methyl-β-keto esters Yield[1] (%)(No.)[2]
1	C_6H_5	-	77 (**163**)
2	$BnO(CH_3)_2C$	40 (**160**)	92 (**164**)
3	*n*-C_4H_9	48 (**161**)	82 (**165**)
4	$BnO(CH_2)_2$	45 (**162**)	72 (**166**)

1. Isolated yield.

2. Compound number.

In the first trial, when 1 mol% of catalyst and β-keto thioester **142** was used and the reaction was carried out under standard conditions for 24 h, surprisingly there was no reduction at all. Initially it was speculated that compound **142** may have been contaminated by thiol because the thioester may be unstable and will release thiol slowly during the transfer hydrogenation reaction. Further increase of the catalyst loading (up to 5 mol%) and using freshly columned substrate also led to no improvement (**Scheme 8**). From this experiment it has been demonstrated that thioesters are stable under HCO_2H/TEA 5/2 conditions and it is not the thiol that poisoned the catalyst. Due to the strong coordination effect of the thioester, catalyst inhibition may happen after catalyst activation (**Figure 70**). Literature reports suggest that the 16-electron Ru (activated (*R,R*)-**c1**) complex is able to coordinate with HCO_2H and isopropanol before the hydrogen transfer happens. Alternatively, thioester coordination with the 16-electron Ru complex

may take place before the hydride is formed. To investigate this hypothesis, propargylic β-keto ester was prepared with only S changed to O.

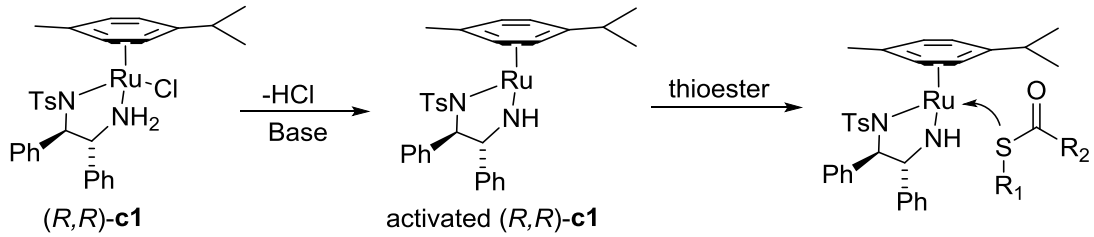
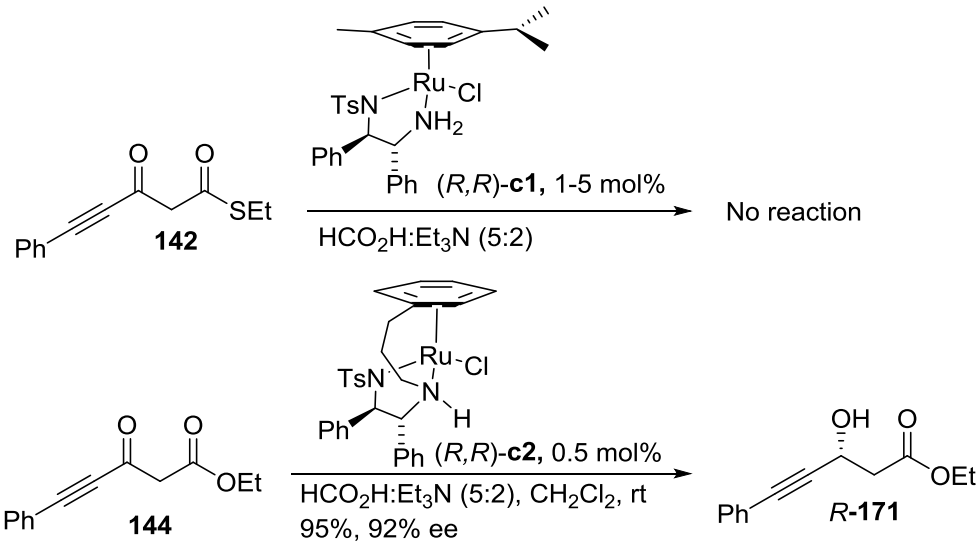


Figure 70. How the thioester poison a catalyst.



Scheme 8. Differing behaviour between propargylic β-keto esters and propargylic β-keto thioesters during the ATH tests.

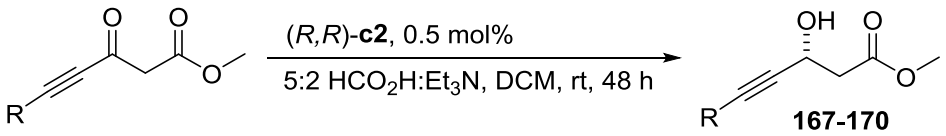
In contrast to the thioester **142**, compound **144** was reduced smoothly under the same conditions by catalyst (*R,R*)-**c2** in high isolated yield (95 %) and excellent ee value (92 %) (**Scheme 8**). The absolute configuration determination and HPLC separation conditions for this compound followed those given in the paper published by Park.[129]

Encouraged by this result, four more propargylic β-keto esters and four propargylic α-methyl-β-keto esters were prepared and tested under these ATH conditions.

All the pure starting materials were found to exist as ketone-enol mixtures (determined by ^{1}H NMR in $CDCl_3$) therefore the concentration of the β-keto esters species was lower than

ketones which do not readily enolize. A 0.5 mol% catalyst loading was chosen to ensure that the reaction was complete in 48 h. Decreasing the catalyst loading to 0.2 mol% (**Table 14**, Entry 1, bracket) gave product **167** in 77% isolated yield after three days along with 9 % of recovered starting material. Unlike aromatic ketones, the experimental results suggest that the propargylic ketones share similar reactivity no matter which R group is present. The reactivity of propargylic ketones is relatively R group-independent; so the same amount of catalyst loading could be applied to all the four substrates (**Table 14**). In general, excellent yields and ee values were achieved in the ATH reactions of propargylic β-keto esters.

Table 14. ATH of propargylic β-keto esters.[1]



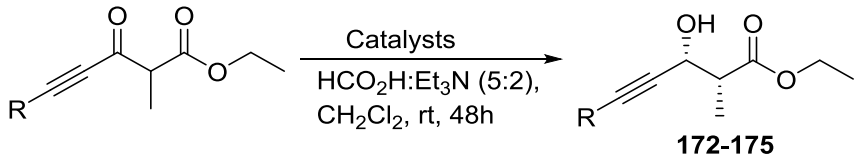
Entry	R(No.)[5]	Yield[2] (%)	Ee[3] (%)
1	C_6H_5 (*R*-**167**)	86(77)[4]	96(96)[4]
2	$BnO(CH_3)_2C$ (*R*-**168**)	99	99
3	*n*-C_4H_9 (*R*-**169**)	92	97
4	$BnO(CH_2)_2$ (*R*-**170**)	92	97

1. The concentration of ketone is 0.15 M and formic acid was used as 5 equivalents.
2. Isolated yield.
3. Ee values were determined by chiral HPLC.
4. Figures in brackets are results when catalyst loading of 0.2 mol% was used.
5. Compound number.

A more ambitious plan was proposed for reducing propargylic α-methyl-β-keto esters using three different catalysts (**c1**, **c2** and **c3**). This time not only enantioselectivities but also diastereoselectivities were examined. Four propargylic α-methyl-β-keto esters were treated with catalysts **c1**, **c2** and **c3** separately. It was found that dr selectivities in

reductions by (*R*,*R*)-**c1** catalyst (up to 31/1) were generally higher than drs in reductions by (*R*,*R*)-**c2** (up to 14/1) and **c3** (up to 13/1) (**Table 15**). From the results obtained using catalysts (*R*,*R*)-**c1** and **c3** it was speculated that the phenyl group on the ligands plays a key role in dr selectivity determination. The higher dr selectivity from catalyst **c1** may result from the physical interaction between phenyl and methyl and ester groups in the transition state (**Figure 71**). Another interesting result came from the use of catalyst **c2**. Although catalyst **c2** possesses a phenyl group the general dr selectivities achieved by catalyst **c2** reduction were close to that of catalyst **c3**. This result suggests that although there is a structural difference between catalysts **c2** and **c3**, the physical interaction with the substrates are similar.

Table 15. Dynamic kinetic resolution of propargylic α-methyl-β-keto esters.



172-175

	Catalyst (*R*,*R*)-**c1**			Catalyst (*R*,*R*)-**c2**			Catalyst ±**c3**		
R(No.)[5]	Yield[2] (%)	Ee[3] (%)	Dr[4]	Yield[2] (%)	Ee[3] (%)	Dr[4]	Yield[2] (%)	Ee[3] (%)	Dr[4]
C_6H_5 (**172**)	99	98	24/1	94	>99	12/1	88	-	11/1
n-C_4H_9 (**173**)	87	99	27/1	92	>99	14/1	21	-	13/1
$BnO(CH_3)_2C$(**174**)	90	99	27/1	97	>99	12/1	-	-	-
$BnO(CH_2)_2$ (**175**)	76	98	31/1	92	>99	14/1	-	-	-

1. The concentration of ketone is 0.15 M and 5 equiv of formic acid was used. Catalyst loadings for **c1** and **c3** are S/C 30/1 for **c2** the loading is S/C 200/1.

2. Isolated yields.

3. Ee values were determined by chiral HPLC.

4. Dr values were determined by ^{1}H NMR using $DCCl_3$ as solvent.

5. Compound number.

Traditionally, the reduction of α-methyl-β-keto ester by Luche reduction ($CeCl_3 \cdot 7H_2O$ and $NaBH_4$) should follow the Felkin Anh model which will preferentially yield the *anti* product.[130] While in the case of Ru-H based dynamic kinetic resolution reaction the *syn* products were formed in a highly selective manner which suggested the reaction went through the transition state (**Figure 71**). From the proposed favoured transition state, it makes no difference when nucleophilic reagents are achiral the two enantiomers reacted at the same rate. But when the nucleophilic reagent is chiral because of the physical interaction between substrate and catalyst, the catalyst will select one enantiomer that can form the lower energy transition state preferentially (**Figure 71**). The excellent enantio and diastereoselectivity stems from both electronic and physical interactions. The existence of the triple bond is equally important for high diastereoselectivity; without this electronic interaction, the dr value will be low.

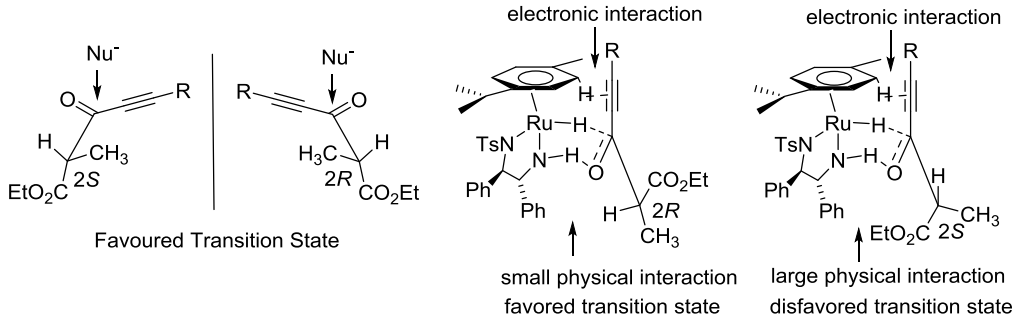


Figure 71. Transition states of transfer hydrogenation DKR.

The dr selectivities were determined by ^1H NMR. From the spectra, it is possible to differentiate and determine the ratios of *syn* product from *anti* clearly by analysis of the integration of their β-protons and the absolute *syn* or *anti* configurations can also be determined by the chemical shifts of the β-protons (**Figure 72**).[131]

Spectrum **1**, **Figure 72** is the compound **172** reduced from the Luche reduction and it is expected that this reduction will slightly favour the formation of the *anti* product. The *syn* product has also been detected as a minor product (*anti*/*syn*=3/1) with a chemical shift that

is higher than the *anti*. Spectrum **2**, **Figure 72** is the same compound reduced by catalyst **c3** in which the dr was determined to be 11/1 in favour of the *syn* configuration. A similar result was achieved using catalyst (*R*,*R*)-**c2** (spectrum **3**) the corresponding dr 12/1 being again in favour of the *syn* product. The highest dr selectivity came from the use of catalyst (*R*,*R*)-**c1** (spectrum **4**, **Figure 72**) which is as high as 23/1.

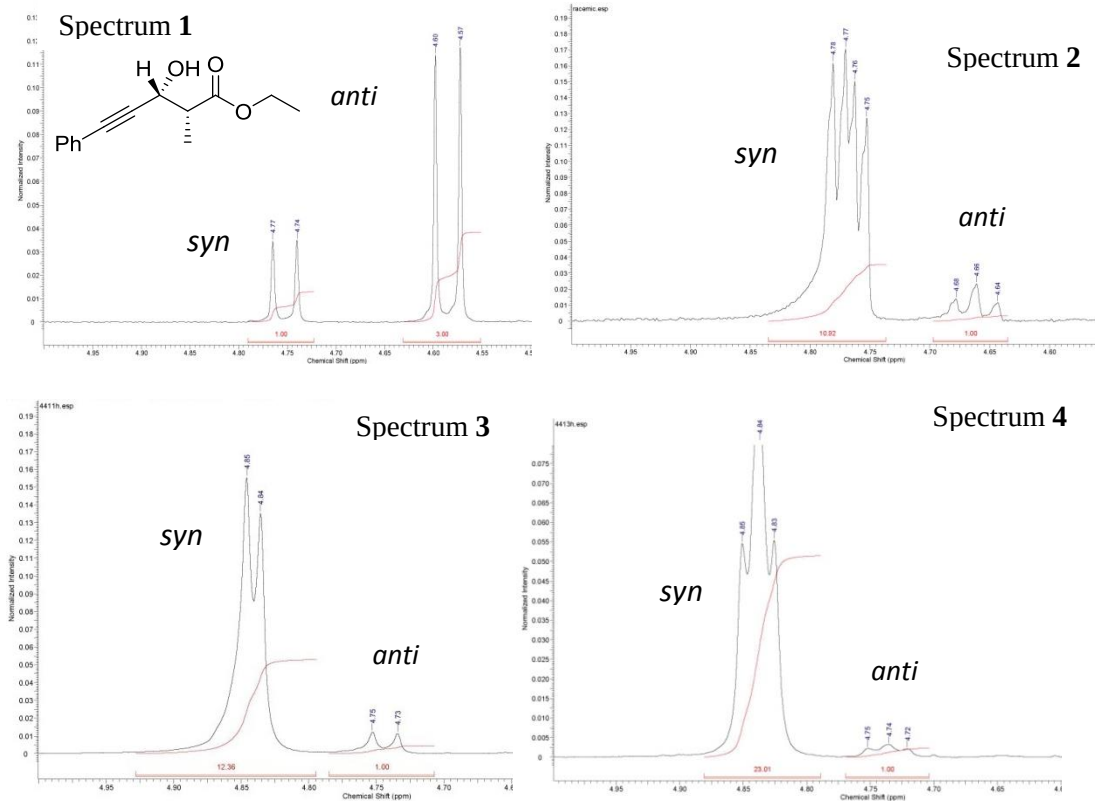


Figure 72. Dr ratios of compound **172** prepared by different methods and catalysts.[1 and 2]

1. ^{1}H NMR (400 MHz) spectroscopic data of β-H were collected in $CDCl_3$.

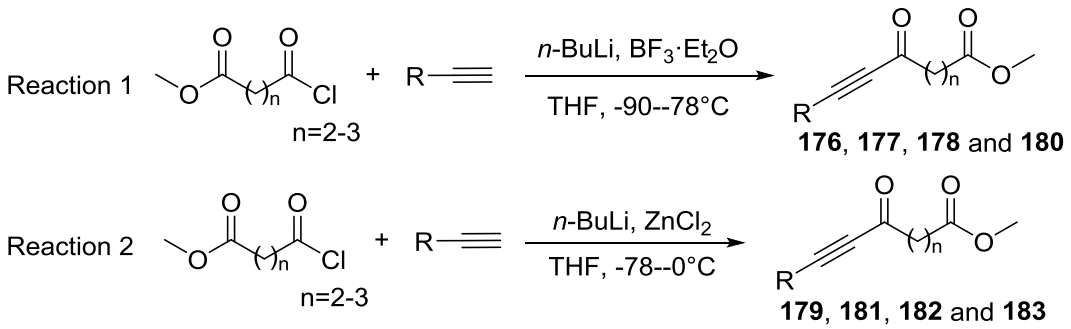
2. Spectrum **1** is compound **172** reduced by Luche reduction. Spectrum **2** is compound **172** reduced by catalyst **c3**. Spectrum **3** is compound **172** reduced by catalyst (*R*,*R*)-**c2**. Spectrum **4** is compound **172** reduced by catalyst (*R*,*R*)-**c1**.

2.2.4. Synthesis of Propargylic γ-Keto Esters and Propargylic δ-Keto Esters and Their ATH Studies.

Propargylic γ-keto esters and propargylic δ-keto esters were prepared by two strategies (**Table 16**). Initially, alkynyl boranes[132] were used as nucleophilic reagents. Compounds

(**176**, **177**, **178** and **180**) were successfully prepared by this method (Reaction 1) but their yields were unsatisfactory (**Table 16**, Entries **2** and **3** n=2). Literature precedent[133] suggests that the *in situ* generated alkynylzinc reagent serving as a mild nucleophilic reagent can react with aliphatic acyl chloride in a very efficient manner. Compounds (**179**, **181**, **182** and **183**) were prepared by this alkynylzinc method and improved yields were observed. From this coupling it was found that the dryness of anhydrous $ZnCl_2$ substantially affected the yields therefore the anhydrous $ZnCl_2$ must be dried under high vacuum at 110 °C for at least 6 h before use. Finally, by using this method, under optimized conditions the product yield could reach 73% (Entry 4, n=3).

Table 16. Synthesis of propargylic γ-keto esters and propargylic δ-keto esters.



		n=2	n=3
Entry	R	Yield[1] (%)(No.)[2]	Yield[1] (%)(No.)[2]
1	C_6H_5	49 (**176**)	43 (**180**)
2	*n*-C_4H_9	27 (**177**)	53 (**181**)
3	$BnO(CH_3)_2C$	22 (**178**)	48 (**182**)
4	$BnO(CH_2)_2$	25 (**179**)	73 (**183**)

1. Isolated yield.

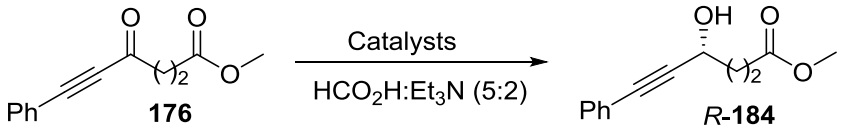
2. Compound number.

Compound **176** was chosen as a representative structure for optimization of the reaction conditions. Solvent effects, different catalysts, catalyst loading and temperature were taken into account during the optimization (**Table 17**). From previous experience in aromatic

ketone transfer hydrogenation, catalysts in CH_2Cl_2 and CH_3CN are equally efficient with respect to reactivities but 4% of enantioselectivity erosion was observed when CH_3CN was employed (**Table 17**, Entries 1 and 2). With regard to catalyst efficiency, one (*R*,*R*)-**c1** could transform 50 equivalents of **176** within 15 h with an excellent ee value of 94%. Catalyst (*R*,*R*)-**c2** was more active and could reduce 500 equivalents of **176** within 30 h. Further decrease of catalyst loading resulted in incomplete conversion of starting material (**Table 17**, Entry 4) even the reaction time was extended to 144 h. From our previous aromatic ketone ATH study, elevated temperature has the beneficial effect of increasing the reaction rate while the enantioselectivity is maintained at the same level. Under this circumstance, rather than accelerate the reaction, the reaction carried out at 30 °C (**Table 17**, Entry 5) gave almost the same conversion and yield as the reaction at room temperature (Entry 4). One interesting phenomenon that was found is that catalyst (*R*,*R*)-**c2** could convert the first 500 molecules of substrates within 30 h but cannot reduce the remaining starting material despite the period of reaction time being extended to 144 h. Combined with the results in Entries 4, 5 and 6 there is reason to believe that the catalyst has been deactivated during the reaction.

It is well known that amines are active nucleophilic reagent that can readily react with propargylic ketones through Michael addition. In that case if the amine ligand has reacted with the starting material by this mechanism it will inevitably cause catalyst inhibition. The explanation for why elevated temperature did not provide better conversion is probably due to the catalyst poisoning process also being accelerated. At room temperature, from the experimental results the activity of catalyst (*R*,*R*)-**c2** can last for more than 7 days in the case of aromatic ketone transfer hydrogenation. The maximum life time of catalyst (*R*,*R*)-**c2** appears to be much shorter and it can only last up to 3 days in the case in **Table 17**.

Table 17. Optimization of reaction conditions.



Entry	Catalyst	Solvent[1]	S/C	T (°C)	Time (h)	Conv[2] (%)	Ee[3] (%)	Yield[4] (%)
1	(*R*,*R*)-**c1**	CH_2Cl_2	50/1	rt	15	100	94 (*R*)	67
2	(*R*,*R*)-**c1**	CH_3CN	50/1	rt	15	100	90 (*R*)	78
3	(*R*,*R*)-**c2**	CH_2Cl_2	500/1	rt	30	100	94 (*R*)	89
4	(*R*,*R*)-**c2**	CH_2Cl_2	1000/1	rt	144	73	95 (*R*)	69
5	(*R*,*R*)-**c2**	CH_2Cl_2	1000/1	30	144	78	95 (*R*)	73
6	(*R*,*R*)-**c2**	CH_2Cl_2	2000/1	40	144	53	94 (*R*)	30

1. The concentration of ketone is 0.15 M and 5 equiv of formic acid was used.

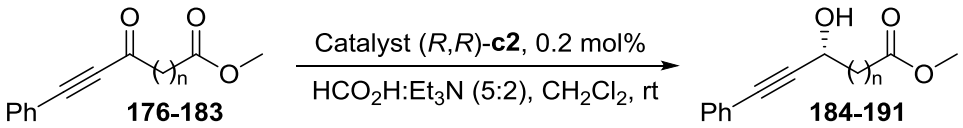
2. Conversions were determined by isolation of starting materials.

3. Ee values were determined by chiral HPLC.

4. Isolated yield.

Taking all these observations into consideration the best reaction conditions were determined to be the use of 0.2 mol % of catalyst (*R*,*R*)-**c2** at room temperature in CH_2Cl_2 solution (**Table 17**, Entry 3). By following these reaction conditions, four propargylic γ-keto esters (**176-179**) and four propargylic δ-keto esters (**180-183**) were tested (**Table 18**). As expected, all the reactions reached full conversion within 72 h using 0.2 mol % of catalyst (*R*,*R*)-**c2**. The reactions proceeded smoothly without forming any by-products (dehydration or lactonization) at any stage of the reaction as assessed by a TLC test. The resulting alcohols (**184-191**) which were formed as the only products were very easy to separate by silica gel column chromatography. HPLC results showed that the reductions of both γ-keto esters and δ-keto esters were equally highly stereoselective and up to 99% ee was achieved in the best case (**Table 18**).

Table 18. ATH of propargylic γ-keto esters and δ-keto esters.



Entry	R(No.)[1]	n	Yield %[2]	Ee %[3]
1	C_6H_5 (*R*-**184**)	2	89	94
2	*n*-C_4H_9 (*R*-**185**)	2	89	93
3	$BnO(CH_3)_2C$ (*R*-**186**)	2	77	99
4	$BnO(CH_2)_2$ (*R*-**187**)	2	95	98
5	C_6H_5 (*R*-**188**)	3	89	96
6	*n*-C_4H_9 (*R*-**189**)	3	81	99
7	$BnO(CH_3)_2C$ (*R*-**190**)	3	84	98
8	$BnO(CH_2)_2$ (*R*-**191**)	3	99	99

1. Compound number.

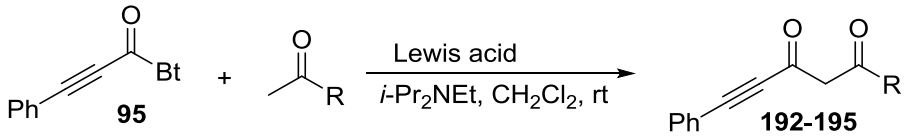
2. Isolated yield.

3. Ee values were determined by chiral HPLC.

2.2.5. Synthesis of 4-Pentyne-1,3-diones and Their ATH Studies.

4-Pentyne-1,3-diketones were prepared by adopting Coltart's soft enolization strategy.[134] Simply by a $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt meditated Claisen-type condensation of Bt-amide and ketone; the 4-pentyne-1,3-diones (**192-195**) were formed in good yield (**Table 19**). Later in the project the strategy was modified by using $Mg(ClO_4)_2$ instead of $MgBr_2 \cdot OEt_2$ which is cheaper and more reasonable for large scale preparation. Although generally a 10% drop in yield was observed when $Mg(ClO_4)_2$ was employed it was still possible to synthesize enough material of good purity for transfer hydrogenation studies.

Table 19. Preparation of 4-pentyne-1,3-diones.



Entry	R(No.)[1]	Lewis acid	Yield[2] (%)
1	Phenyl(**192**)	$MgBr_2 \cdot OEt_2$	81
2	4-Methylphenyl(**193**)	$Mg(ClO_4)_2$	66
3	4-Methoxyphenyl(**194**)	$Mg(ClO_4)_2$	72
4	2-Furanyl(**195**)	$Mg(ClO_4)_2$	61

1. Compound number.

2. Isolated yield.

The ATH of 1,3-diketones is relatively slow because most of the substrates exist in the enol form in solution which is inactive to catalyst.[62] From our ^{1}H NMR study, more than 95% of compound **192** exists as the enol in $CDCl_3$. Since the 1,3-diketone and enol ketone exist in a dynamic equilibrium, with the consumption of the diketone more enol ketone will converted to diketone through the equilibrium which will eventually lead to the complete conversion of all the starting material to product.

Under standard reduction conditions (HCO_2H/TEA 5:2 in CH_2Cl_2, 10 mol% of (*R*,*R*)-**c1**, 0.15 M of diketone) 1,5-diphenyl-4-pentyne-1,3-dione **192** was completely consumed within 12 h. However the R_f of the product from ATH reaction did not match the R_f of the racemic sample from the literature.[135] The product **196** from reaction mixture was isolated and the structure has been assigned (**Figure 73**) by comparing the ^{1}H NMR data with that reported for this compound in the literature (in the ^{1}H NMR of the compound, all the protons can be assigned to aromatic and alkenic proton).[136]

Soon it was discovered that compound **192** is very sensitive to acid or base. When treated with HCO_2H/TEA 5:2 it is able to completely cyclize within 12 h (**Figure 73**). From the stability tests the same cyclization reaction in TEA was even faster and was completed in

3 h. Considering that catalysts **c1** and **c2** have no way of competing with the cyclization that happens so rapidly in HCO_2H/TEA5:2 solution, the only option is to use base free conditions to stop the cyclization. Subsequently 10 mol% of activated catalyst (*R*,*R*)-**c1** was loaded into an isopropanol solution of diketone **192** (0.15 M) at room temperature; surprisingly even under these base-free conditions the intramolecular cyclized product **196** can still be observed in considerable quantities despite mild reaction conditions but still no diol could be found in the reaction mixture.

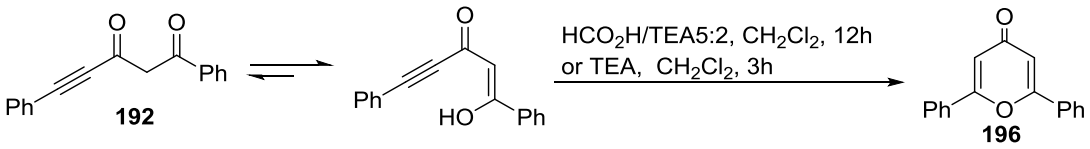


Figure 73. Decomposition by intramolecular cyclization of diketone **192**.

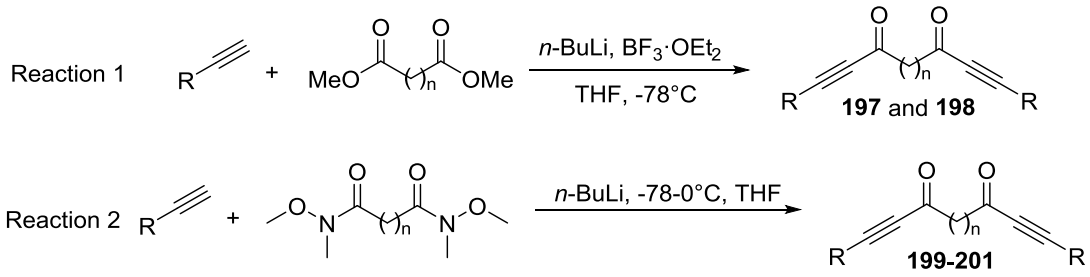
According to Cossy,[137] aromatic 1,3-diketones are good substrates for transfer hydrogenation. Reportedly, in the case of 1,3-diphenyl-propan-1,3-dione, under optimized conditions (5.0 mol% of (*R*,*R*)-**c1**, HCO_2H/TEA 5:2, CH_2Cl_2 at 50°C) it could be fully reduced within 3.5 h. At room temperature the reaction still proceeds but at a slower rate (48 h to reach completion). Compared to aromatic 1,3-diketones although propargylic 1,3-diketones are known to be more sensitive, the reason why they are not active to even as much as 10 mol% of (*R*,*R*)-**c1** may be due to the very high proportion of enol isomer in the mixture (enol/ketone=35/1 in $CDCl_3$).

Since the properties of 4-pentyne-1,3-dione and the ATH reaction conditions are not compatible, attention was focussed instead on propargylic 1,4-diones and 1,5-diones in the hope that the structural changes would bring a beneficial effect.

2.2.6. Synthesis of Propargylic 1,4-Diketones and Propargylic 1,5-Diketones and Their ATH Studies.

Propargylic 1,4-diketones and propargylic 1,5-diketones were prepared by two strategies (**Table 20**). The first one is the direct attack by alkynyl borane. From this reaction it was found that the reactivity of diesters is not high enough; after work-up there was still a large amount of diester starting material remaining unreacted. After work-up the resulting solution was actually a mixture of diester, mono-replaced keto ester and diketone. The yields (**Table 20**, Entries 1 and 2) are disappointingly low because most of the diester was unreacted. Additional difficulty was caused by the similar polarities of diester and diketone; significant efforts were required to separate the diketone from the diester by column chromatography. The low efficiency of this reaction required the consideration of other alternatives and a precedent using a Weinreb amide as starting material was found.[138] Indeed not only were side reactions minimized by using the Weinreb amide, it is more likely that the Weinreb amide reacted with two molecules of alkynyl lithinates to result in complete conversion and higher yields. Even if there was still Weinreb diamide unreacted, the polarity difference between the diamide and the resulting propargylic diketone is enough to ensure a facile separation. Some propargylic diketones are unstable (**Table 20**, Entries 6 and 7) at room temperature and decomposed on the silica gel column therefore rendering the preparation impossible. Despite the elusive nature of propargylic diketones, five examples were prepared for evaluation in ATH studies.

Table 20. Synthesis of propargylic 1,4-diketones and propargylic 1,5-diketones by two different methods.



Entry	R(No.)[1]	n	Yield[2] (%)	Method
1	C_6H_5 (**197**)	2	26	Reaction 1
2	C_6H_5 (**198**)	3	17	Reaction 1
3	$BnO(CH_3)_2C$ (**199**)	2	43	Reaction 2
4	$BnO(CH_3)_2C$ (**200**)	3	79	Reaction 2
5	*n*-C_4H_9 (**201**)	2	92	Reaction 2
6[3]	*n*-C_4H_9	3	0	Reaction 2
7[3]	$BnO(CH_2)_2$	2	0	Reaction 2

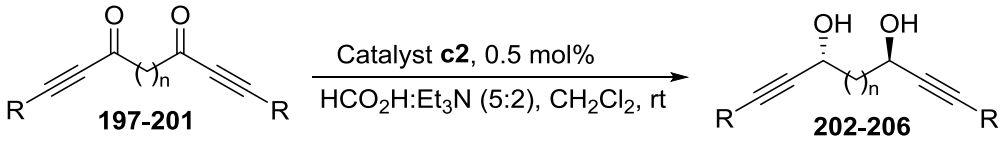
1. Compound number.

2. Isolated yield.

3. In Entries 6 and 7, compounds are thermodynamically unstable at room temperature.

The five propargylic diketones (**197**-**201**) are stable at room temperature and in HCO_2H/TEA(5/2)/CH_2Cl_2 solution for several days. The transfer hydrogenation reaction was carried out under the same conditions that were used to reduce propargylic γ-keto esters and δ-keto esters. ^{1}H NMR spectra illustrate that these diketones can exist predominantly in the ketone form (ketone/enol > 20/1 in $CDCl_3$) and therefore should be reduced easily. Based on this analysis, the catalyst loading was chosen as 0.5 mol%. From the results shown in **Table 21**, the reactivities of 1,4-diketones and 1,5-diketones are similar and both of them were fully reduced within 48 h. Since in the reduction each of the diketones has been selected twice the ee values were expectedly high. In all the cases ee values were higher than 99% and de values were also excellent (all are above 93%).

Table 21. ATH of propargylic 1,4-diketones and 1,5-diketones.



Entry	Catalyst	R(No.)[5]	n	Yield[2] (%)	Ee[3] (%)	De[3] (%)
1	(*R*,*R*)-**c2**	C_6H_5 (*R*,*R*-**202**)	2	81	>99%	93
2	(*R*,*R*)-**c2**	*n*-C_4H_9 (*R*,*R*-**203**)	2	87	>99%	95
3	(*R*,*R*)-**c2**	$BnO(CH_3)_2C$ (*R*,*R*-**204**)	2	83	>99%	96
4	(*R*,*R*)-**c2**	C_6H_5 (*R*,*R*-**205**)	3	96	>99%	97
5	(*R*,*R*)-**c2**	$BnO(CH_3)_2C$ (*R*,*R*-**206**)	3	86	>99%	97
6	(*S*,*S*)-**c2**	C_6H_5 (*S*,*S*-**202**)	2	78	>99%	96
7	(*S*,*S*)-**c2**	*n*-C_4H_9 (*S*,*S*-**203**)	2	82	>99%	93
8	(*S*,*S*)-**c2**	$BnO(CH_3)_2C$ (*S*,*S*-**204**)	2	70	>99%	98
9	(*S*,*S*)-**c2**	C_6H_5 (*S*,*S*-**205**)	3	81	>99%	97
10	(*S*,*S*)-**c2**	$BnO(CH_3)_2C$ (*S*,*S*-**206**)	3	97	>99%	98

1. The concentration of ketone is 0.15 M and 10 equiv of formic acid were used.

2. Isolated yield.

3. Ee values and de values were determined by chiral HPLC.

4. When (*S*,*S*)-**c2** was used the absolute configuration of products are (*S*,*S*).

5. Compound number.

Another difficulty raised by the chiral diols is the determination of ee and de values. Since the ^1H chemical shifts exhibit no difference between chiral and *meso* diols it was not possible to determine the de value by proton NMR. Fortunately the mixture of (*R*,*R*)-diol, (*S*,*S*)-diol and *meso*-diol could be easily separated by HPLC. Under these circumstances, all five propargylic diketones (**197**-**201**) were treated with (*R*,*R*)-**c2** and (*S*,*S*)-**c2** to prepare (*R*,*R*) and (*S*,*S*) HPLC samples. The results are summarized in **Table 21**, comparing the results achieved from (*R*,*R*)-**c2** and (*S*,*S*)-**c2** catalysts; with the exception of the absolute configuration of diols, the yields, ee and de values were almost identical. It has been proved that propargylic diketones with chain numbers n = 2 and 3 are good substrates for transfer hydrogenation under HCO_2H/TEA conditions. The reaction is highly efficient and

selective during the course of the reduction and no intramolecular cyclization (shown in **Figure 74**) was observed at any stage.

A stability test was carried out before the propargylic diketone transfer hydrogenation tests on the 1,4 and 1,5 diketones. Ketone **207** was chosen to test its stability in typical reduction conditions. It was found that after 12 h in HCO_2H/TEA (5/2)/CH_2Cl_2 solution all the starting material had been consumed but cyclised and dimerized products were identified by EI-MS (**Figure 74**). Fortunately the HCO_2H/TEA (5/2) unstable compound **207** could be fully reduced in isopropanol under aforementioned base free conditions. When studying the 1,4-diketone reduction in HCO_2H/TEA it is encouraging that primary alcohol and secondary alcohol did not share the same stabilities. As shown in **Figure 74** the primary alcohol **207** is readily cyclised through an intramolecular Michael addition. The secondary alcohol intermediate which results from mono-reduction of the diketone is more stable than primary alcohol. So it can be concluded that the nucleophilic ability of the secondary alcohol is not as high as that of the primary alcohol. Even at the end of the transfer hydrogenation in **Table 21**; no cyclised or dimerized product can be found, thus allowing the slightly acidic HCO_2H/TEA conditions to be employed to reduce the 1,4-diketones and 1,5-diketones.

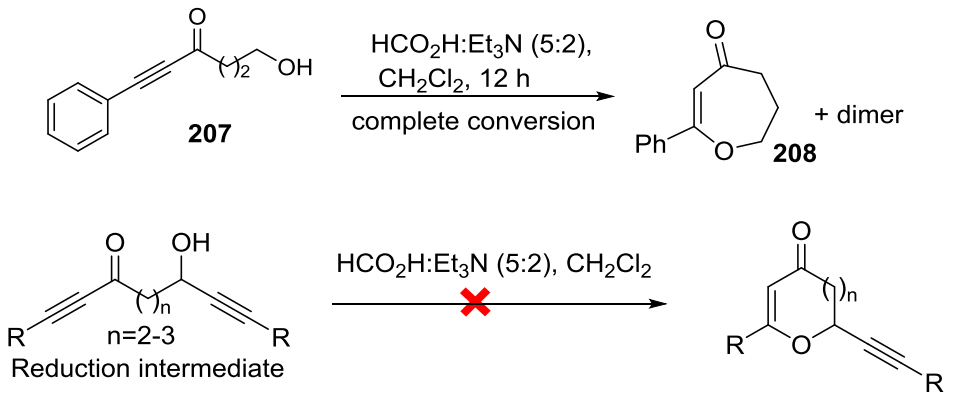


Figure 74. Possible intramolecular cyclization as a side-reaction.

2.2.7. Asymmetric Total Synthesis of (-)-Yashabushidiol B.

The chiral β-hydroxy-γ-alkynyl ester scaffold is a very versatile building block because both sides of the chiral centre have functional groups which can be modified or extended easily. As illustrated in **Figure 75**, overall hydrogenation by Pd/C and Pt is a very convenient and high yielding way to unveil CH_2CH_2 from C≡C which has been adopted at the beginning of the total synthesis of (-)-yashabushidiol B in this project. The alkyne unit can also be hydrogenated to the (Z)-alkene by a well established Lindlar catalyst catalyzed hydrogenation. The alkene can be further modified by other reactions such as ozone oxidation and Sharpless asymmetric dihydroxylation. Furthermore if the R_1 group is a silyl group then it can be easily removed to release the terminal alkyne or replaced bromine in a desilylbromination reaction.

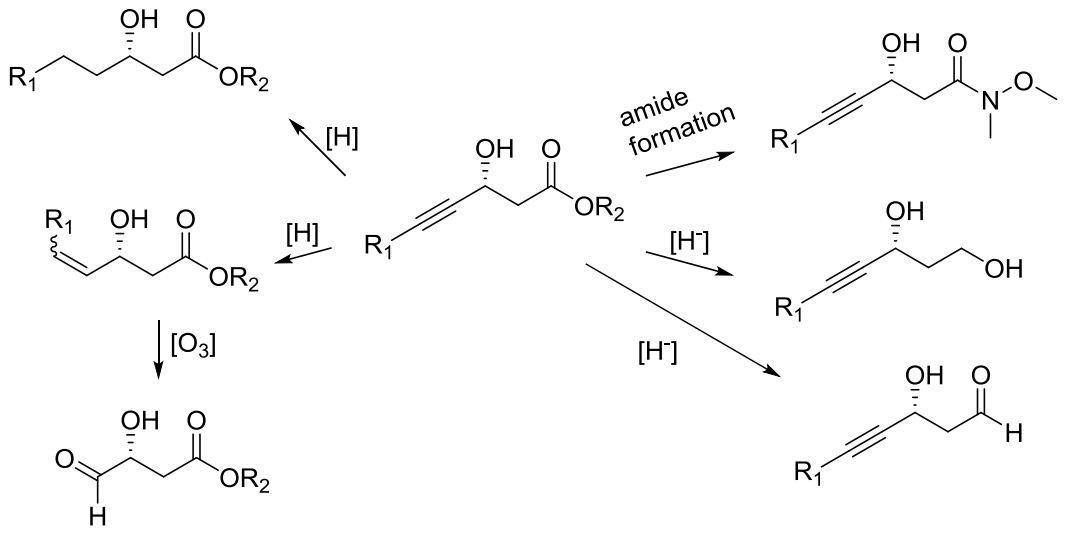


Figure75. Modification of β-hydroxy-γ-alkynyl ester.

The ester unit can be used as the precursor of a Weinreb amide or aldehyde which could couple with a nucleophilic reagent such as Grignard reagents, enol or silyl enol ethers. The β-hydroxy-γ-alkynyl ester scaffold which could be prepared by ATH on a gram scale and high optical purity easily may therefore be applied broadly in target related synthesis.

The asymmetric formal synthesis and biological activity of (-)-yashabushidiol B was reported by Yang.[139] From his report the enantiopure (-)-yashabushidiol B could be

obtained from hydrogenation of another natural compound; (3*R*,5*S*)-trans-3,5-dihydroxy-1,7-diphenyl-1-heptene. From his paper, (-)-yashabushidiol B has been proved to possess anti-emetic effects in young chicks (50 mg/kg, 47% inhibition).

The total synthesis of (-)-yashabushidiol B has been reported by Shinde by using the chiron approach.[140] From the chiral building block which was prepared from D-glucose, 5 extra steps were required to reach completion. The data of the synthetic (-)-yashabushidiol B as well as the natural one provide beneficial references for the total synthesis study and structure determination in this project.

Another route for the total synthesis of (-)-yashabushidiol B has been developed by Venkateswarlu.[141] A chiron approach was also used, the chiral source being D-mannitol. From his paper, a total of 12 steps were required to build the full skeleton of (-)-yashabushidiol B. Biological evaluation shown that (-)-yashabushidiol B was not highly functional against cancer cell lines (IC_{50} values THP-1 (99.75 μg/mL) U-937 (128.25 μg/mL) A-375 (144.75 μg/mL)).

The synthetic plan towards (-)-yashabushidiol B is extremely simple and straightforward. The chiron approach was discarded in favour of catalytic asymmetric synthesis to build the chiral centres of (-)-yashabushidiol B. The retrosynthesis is shown in **Figure 76**. From the knowledge of the diketone reduction it was known that the C2 symmetry of (-)-yashabushidiol B could not be built from compound **209** by transfer hydrogenation. Since the double transfer hydrogenation is not applicable to propargylic 1,3-diketones it is necessary to install the chiral hydroxyl groups sequentially. This approach required five steps including two highly efficient hydrogenation reactions and one stereoselective transfer hydrogenation from compound *R*-**171**. Both the chiral hydroxyl groups (1,3-diol) can be introduced by transfer hydrogenation. This strategy is also a protective group-free one; the first introduced hydroxyl group can survive five synthetic steps without protection.

The free hydroxyl group did not jeopardize the yield of each reaction or the dr values of the second transfer hydrogenation. In addition, no dehydration or racemisation was observed.

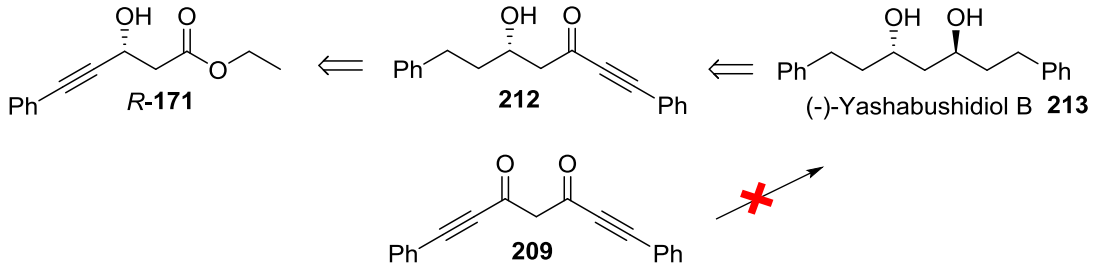
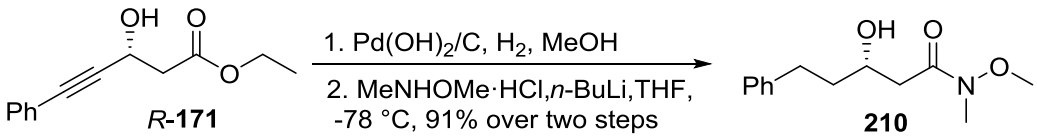


Figure 76. Retrosynthesis of (-)-yashabushidiol B.

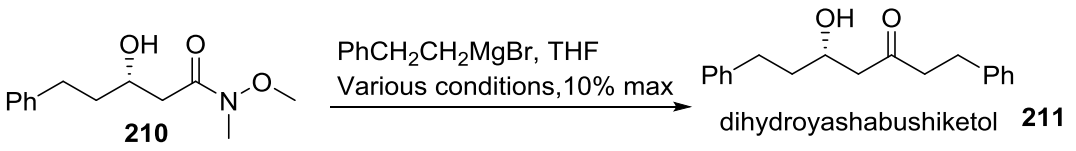
The triple bond of compound *R*-**171** (92% ee) was reduced within 1 h by a $Pd(OH)_2/C$ catalysed hydrogenation at 1 atm H_2 atmosphere. The crude product was found to be pure enough to be used directly in the next step without purification. Subsequent Weinreb amide formation proceeded smoothly and the product **210** was formed in 91% yield over two steps (**Scheme 9**). This Weinreb amide formation reaction was achieved without the need for hydroxyl group protection and gave the desired compound as a single product.



Scheme 9. Synthesis of Weinreb amide **210**.

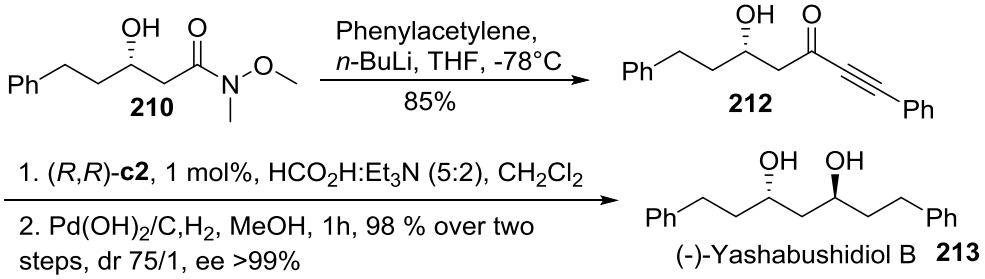
The method from **Scheme 9** allowed up to 300 mg of intermediate **210** to be readily prepared. With sufficient Weinreb amide in hand, the ketone formation was attempted under a range of different conditions. Literature precedent[142] suggested that decent yields could be achieved when coupling the β-hydroxyl Weinreb amide with a Grignard reagent or alkyllithium. However the coupling between **210** and a Grignard reagent proved to be troublesome, and a maximum of 10% yield, in medium purity, of dihydroyashabushiketol **211** was obtained (**Scheme 10**). From

TLC it was found that extension of the reaction time or an increase in the loading of Grignard reagent (minimum 3 equiv to maximum 7 equiv) resulted in disappearance of the product spot. Since all starting material had disappeared, it was speculated that the coupled intermediate is not stable under the strong basic conditions used.



Scheme 10. Synthesis of dihydroyashabushiketol **211**.

An alternative route (**Scheme 11**) was required to replace the use of Grignard reagent. The formation of ketone **212** was achieved through a published procedure,[143] when phenylacetylene lithinate were used at low temperature (-78 °C) the triple bond-containing product **212** was obtained in 85% yield without decomposition. The second chiral hydroxyl group was installed by (*R*,*R*)-**c2** catalyzed asymmetric transfer hydrogenation. After work-up the resulting crude diol was hydrogenated directly using $Pd(OH)_2/C$ (20% w/w) to gave the final product (-)-yashabushidiol B in excellent yield (98% from two steps). During the course of the second ATH reaction there was no evidence of starting material **212** self-condensation, although reportedly these materials structurally similar with **212** are unstable under acidic conditions.[144]



Scheme 11. Complete the synthesis of (-)-yashabushidiol B.

The experimental data for the synthetic (-)-yashabushidiol B formed by this route

matched that for the natural (-)-yashabushidiol B and synthetic (-)-yashabushidiol B prepared by the Shinde group.[140] The detailed spectroscopic data are listed in the experimental section.

The dr of (-)-yashabushidiol B was determined to be >20/1 by ^{1}H NMR (**Figure 77**) but the ee value of this compound was still undetermined because of the lack of a racemic standard. From the knowledge of 1,4 and 1,5-diketone reduction, if the substrate was stereoselectively reduced twice by (*R*,*R*)-**c2** catalyst the ee value should be above 99% but how the chiral β-hydroxyl group will affect the diastereoselectivity is unknown. The racemic standard was prepared by the procedure shown in **Scheme 12** from commercially available 3-phenyl propionaldehyde **214**. From the ^{1}H NMR analysis of the racemic sample **213** it was surprisingly found that the ratio of *anti*/*meso* is 5/1 and this result was further confirmed by HPLC. Since the final diol was from the ATH of racemic **212** by using racemic **c1** (ca. 1/1 mixture of (*R*,*R*)-**c1** and (*S*,*S*)-**c1** formed by combining the optically pure catalysts) the result suggested that the *anti*-diol formation was 5 times as fast as *meso*-diol formation. From the HPLC results, it was established that (-)-yashabushidiol B had been formed with >99% ee and 75/1 dr in the asymmetric synthesis.

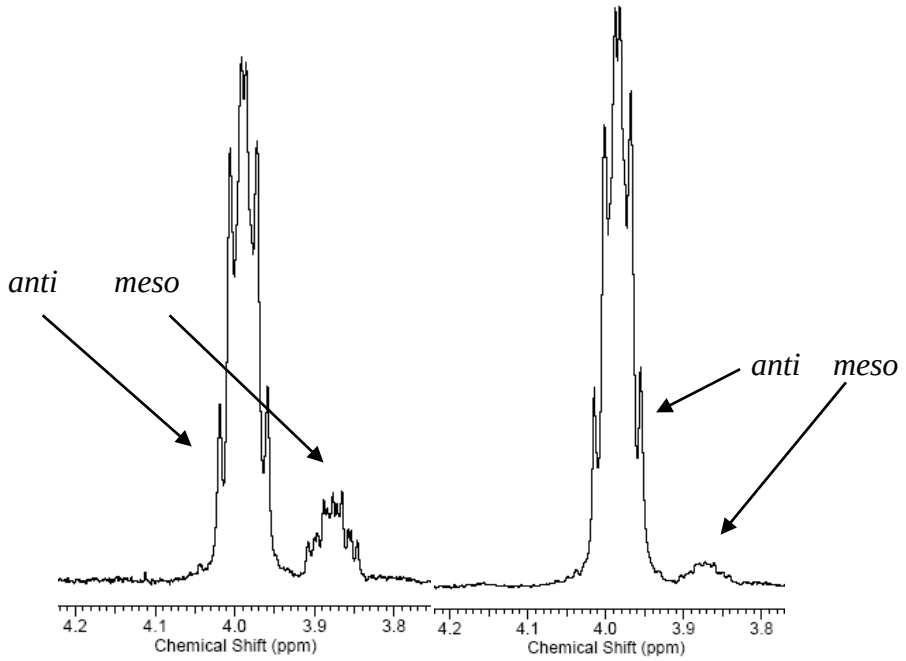
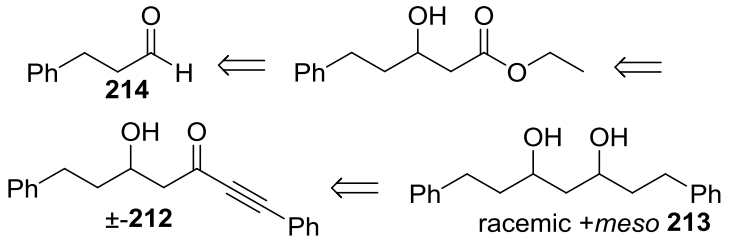


Figure 77. ^{1}H NMR chemical shift of (-)-yashabushidiol B C3-H[1].

1. Left figure: racemic standard from the racemic procedure. Right figure: (-)-yashabushidiol B from the asymmetric process.



Scheme 12. Synthesis of racemic yashabushidiol B.

2.3. Asymmetric Transfer Hydrogenation of Diynones.

2.3.1. Synthetic Design.

As was the case with the work of asymmetric propargylic ketone reduction, some interesting questions were raised such as: can chiral diynols be prepared by ATH? Will the diynones exhibit the same behaviour as the ynones which were previously studied? To date, the only catalytic pathway to the chiral diynol scaffold is through asymmetric 1,3-diyne addition to aldehydes. The advantages of this method include straightforward

pathway design, broad substrate scope and the low cost of catalyst. However the requirement for the use of a 1,3-diyne in large excess, coupled to the fact that 1,3-diynes may be difficult to prepare and in some cases are unstable, inevitably makes this reaction less efficient. Other drawbacks, for example that the enantioselectivity is highly dependent on the structures of the aldehydes, make it difficult to optimize reaction conditions.

As a part of the propargylic ketone ATH project it seemed desirable to introduce an alternative route to the synthesis of the chiral diynol scaffold. More interestingly, the chiral diynol scaffold has also been found in a number of natural products. In literature, diynone intermediates appear not to be accessible through the reaction of 1,3-diynes and Weinreb amides no matter which bases (*n*-BuLi, *t*-BuLi or LiNHMDS) are used (**Figure 78**).[145] Also, 1,3-diynes are unstable species; very difficult to prepare and purify in a large scale, and some are too volatile for manipulation. Therefore the application of 1,3-diynes has been limited. Although transfer hydrogenation is highly efficient, an inefficient reaction before the ATH will have an adverse influence on the overall efficiency and will reduce the value of the applications. Since asymmetric 1,3-diyne addition is a published reaction there is probably little advantage to begin from making racemic diynols by 1,3-diyne addition. Due to the problems associated with 1,3-diynes and balancing all the synthetic routes at the design stage, their use should be avoided if possible.

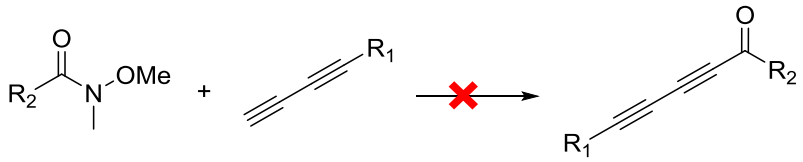


Figure 78. Unsuccessful approach to diynones.

2.3.2. Synthesis of Diynone Precursors.

Chiral diynols can be obtained by three consecutive reactions from the design shown in **Figure 79**. The racemic diynols could be prepared from corresponding alkynes and

bromoalkynes. The successful preparation of bromoalkynes is a well established route. They can be obtained in large scales (form 5.0 mmol to 0.2 mol) and with good purity without the need for column purification. In contrast to 1,3-diynes, bromoalkynes are not volatile, relatively stable and easy to manipulate at room temperature.

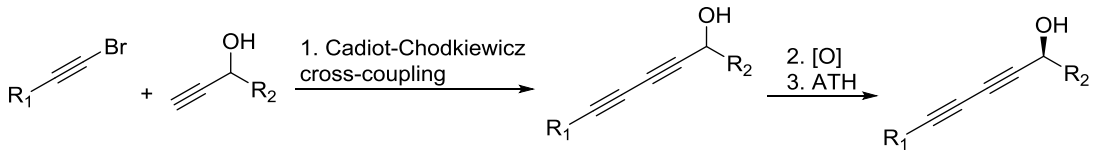


Figure 79. Synthetic plan for preparation of chiral diynols.

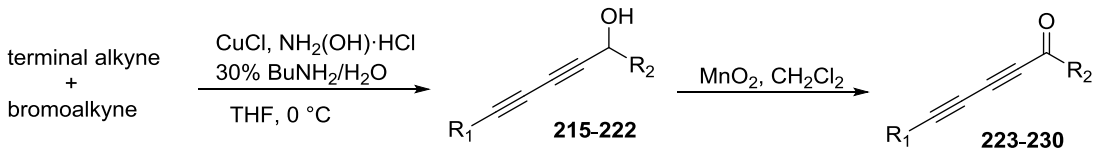
The synthesis of diynones commenced from the coupling reaction between a terminal alkyne and a bromoalkyne. As shown in **Table 22** the first step requires a well established Cadiot-Chodkiewicz cross-coupling which has been proved to be one of the most efficient ways of forming 1,3-diyne species. In the Cadiot-Chodkiewicz reaction described, racemic 1-yne-3-ols are used as coupling reagents which are either commercially available or easily accessible via organic synthesis. The oxidation of diynols to diynones is unknown and for this reason a strategy (MnO_2 oxidation)[146] commonly used to oxidize ynols to ynones was applied to this system. Finally, a catalytic ATH which works very well in ynone reduction would be used directly and it was hoped that that in the case of diynones the same level of efficiency and enantioselectivities would be maintained.

Eight racemic diynols (**215**-**222**) containing different R_1 and R_2 groups were prepared by the Cadiot-Chodkiewicz cross-coupling (**Table 22**, Reaction 2). Diynols were formed in good to excellent yields (72-98%) as single products. No bromoalkyne-bromoalkyne cross coupling was observed in the Cadiot-Chodkiewicz reaction. After purification, the resulting diynols were oxidized by activated MnO_2 powder (**Table 22**, Reaction 2).

With the exception of **Table 22**, Entry 6, in all the other cases clean diynones (**223**-**230**) were formed as the only products by TLC analysis and were easily isolated using silica gel column chromatography. Activated MnO_2 power can oxidize diynols preferentially

without breaking the electron-rich 1,3-diyne bond or oxidizing the terminal hydroxyl (**Table 22**, Entry 5). In Entry 6, when R_2 is equal to $CH_2C_6H_5$ the resulting ketone is more likely to enolize than the rest, therefore it could be further oxidized by MnO_2 which would explain why the yield in Entry 6 is much lower than the others. In Entry 3 pure diynone **225** has not been separated because it is highly volatile and was used subsequently as a CH_2Cl_2 solution.

Table 22. Synthesis of diynones.



Entry	R_1	R_2	Step 1 Yield[1] (%)/(No.)[3]	Step 2 Yield[1] (%)/(No.)[3]
1	C_6H_5	CH_3	90 (**215**)	98 (**223**)
2	$BnO(CH_3)_2C$	CH_3	79 (**216**)	85 (**224**)
3	*n*-C_4H_9	CH_3	69 (**217**)	- (**225**)[2]
4	*n*-C_4H_9	*n*-C_3H_7	88 (**218**)	82 (**226**)
5	$HO(CH_2)_4$	CH_3	98 (**219**)	90 (**227**)
6	*n*-C_4H_9	$CH_2C_6H_5$	72 (**220**)	25 (**228**)
7	$BnO(CH_2)_5C$	CH_3	97 (**221**)	71 (**229**)
8	$BnO(CH_3)_2C$	*i*-C_3H_7	73 (**222**)	98 (**230**)

1. Isolated yield.

2. This compound was not isolated.

3. Compound number.

2.3.3. Asymmetric Transfer Hydrogenation of Diynones.

Initially, 6-phenyl-3,5-hexadiyn-2-one **223** was selected as an example for testing in order to establish its behaviour in the ATH reaction. It was quickly found that the ATH of this

compound is problematic. Ketone **223** is not only sensitive to TEA or HCO_2Na but also a disfavoured side reaction was detected during attempts at ATH.

A standard ATH reaction using compound **223** was carried out and monitored by ^1H NMR. After the reaction, peaks were observed at 5.4 and 6.3 ppm which were identified as belonging to alkene. TLC showed a spot close to the spot of 6-phenyl-3,5-hexadiyn-ol **215**. Based on this result it was believed that a competing hydrogen transfer process takes place on the dialkyne (**Figure 80**).

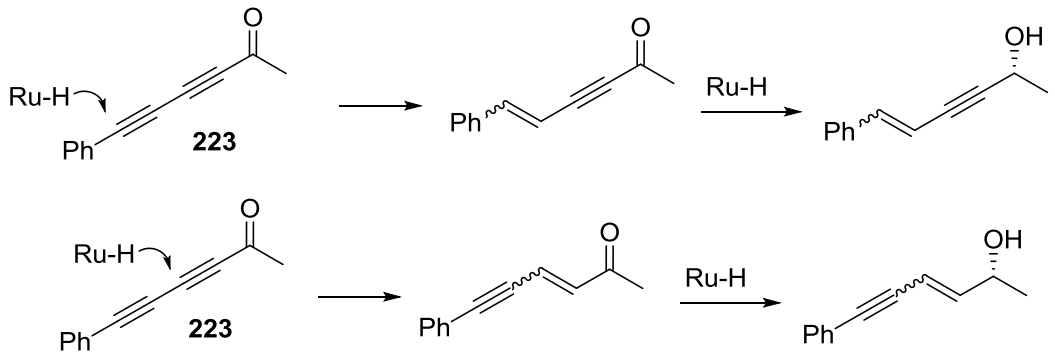


Figure 80. Possible pathway of side reactions.

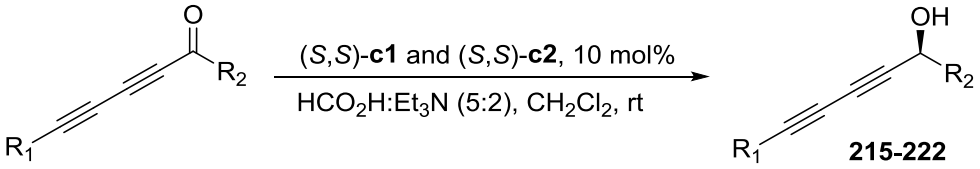
In contrast to 6-phenyl-3,5-hexadiyn-2-one **223**, when the rest of the ketones were tested there were almost no decomposition or alkyne reduction observed during ATH. The structure of the side-products shown in **Figure 80** were not isolated or determined therefore the position of addition of the Ru-H is not known. Although the yield of *S*-**215** is low (25%) the ee from the isolated product was 94% which is still very encouraging (**Table 23**, Entry 1).

Considering that the reduction of alkyne and carbonyl are competing reactions, it was reasoned that installing a bulky group at the end of the diyne may slow down the rate of alkyne reduction. Ketone **224** bearing a $BnO(CH_3)_2C$ group (**Table 22**, Entry 2) was tested under the same conditions. Surprisingly this compound **224** was not only stable in HCO_2H/TEA 5:2/CH_2Cl_2 solution but also only a trace amount (<5%) of the alkyne

reduction product was detected in the ^{1}H NMR spectrum. It appears that the R_1 group on the diyne side plays a key role in determining the behaviour of the substrates.

The relatively low stabilities of diynones required an increase of the catalyst loading to 10 mol% to allow the reaction to finish within a few hours (1 h when (*S*,*S*)-**c2** was used, 3 h when (*S*,*S*)-**c1** was used). The reduction of diynones with an aliphatic chain gives both excellent yield (up to 95%) and ee (up to 99%). In **Table 23**, Entry 5 even with a free hydroxyl group on the side of R_1 group, neither the yield nor the selectivity of the reduction is compromised.

Table 23. ATH of diynones.



Entry	R_1	R_2/(No.)[4]	Yield[1,3] (%)	ee[2,3] (%)
1	C_6H_5	CH_3 (*S*-**215**)	25	94
2	$BnO(CH_3)_2C$	CH_3 (*S*-**216**)	86(82)	94(93)
3	*n*-C_4H_9	CH_3 (*S*-**217**)	94(75)	97(97)
4	*n*-C_4H_9	*n*-C_3H_7 (*S*-**218**)	91(95)	97(98)
5	$HO(CH_2)_4$	CH_3 (*S*-**219**)	89(96)	>90 (>90)
6	*n*-C_4H_9	$CH_2C_6H_5$ (*S*-**220**)	90(92)	97(98)
7	$BnO(CH_2)_5C$	CH_3 (*S*-**221**)	85(76)	95(90)
8	$BnO(CH_3)_2C$	*i*-C_3H_7 (*S*-**222**)	79(95)	96(99)

1. Isolated yield.

2. Ee values were determined by chiral HPLC.

3. Figures in brackets are yields and ees achieved by using catalyst (*S*,*S*)-**c2**.

4. Compound number.

2.3.4. Asymmetric Total Synthesis of Panaxjapyne A.

Panaxjapyne A-C were isolated in 2010 as secondary metabolites from the roots of *Panax japonicus* C. A. Meyer var. *major* alongside four other closely structurally related compounds. The structure of panaxjapyne A was determined by extensive NMR and HRMS studies. Structurally, panaxjapyne A combines a highly light and heat-sensitive diyneol and a skipped enyne subunit which are quite synthetically challenging to construct (**Figure 81**). In this section, a catalytic asymmetric transfer hydrogenation reaction of diynones is described, which allows panaxjapyne A to be an ideal target to demonstrate the power of diynone ATH.

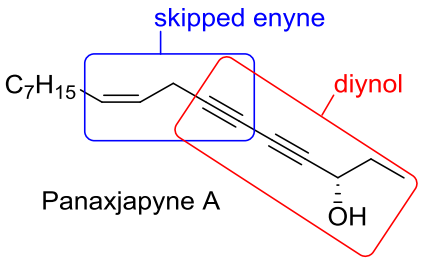


Figure 81. The composition of panaxjapyne A.

To build the full skeleton of panaxjapyne A, the synthetic plan was to first obtain the key intermediate, a skipped enyne **234**. Then by a well-established and reliable desilyl-bromination and Cadiot-Chodkiewicz cross-coupling reaction, it will be possible to build the full structure of racemic panaxjapyne A (**Figure 82**). Since a very efficient method for converting the racemic diynol to enantio-enriched one has been developed, it was anticipated that the late stage installation of the C-3 chirality would be possible without significant difficulty.

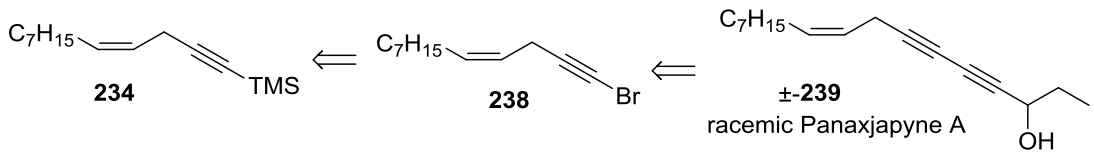
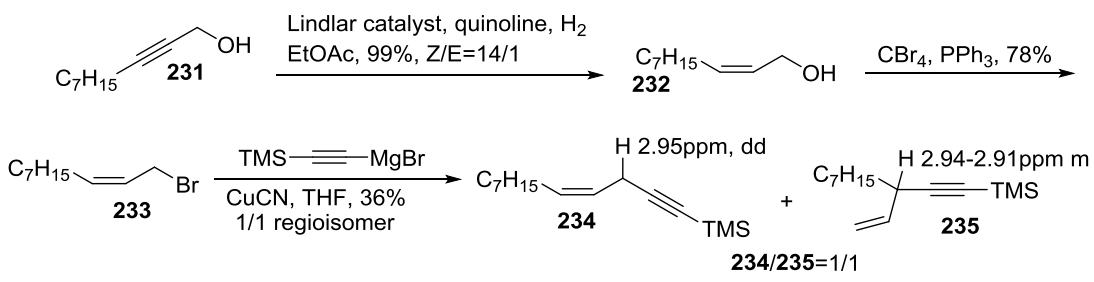


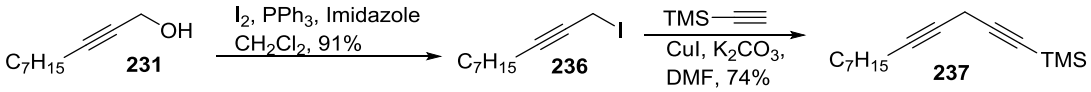
Figure 82. Retrosynthesis of panaxjapyne A.

The initial attempt at making the key intermediate **234** started from commercially available 2-decyn-1-ol **231** (**Scheme 13**). Compound **233** was prepared by known procedures. Treatment of alcohol **231** with Lindlar's catalyst and quinoline under a 1 atm H_2 atmosphere afforded the (Z)-alkene **232** in excellent yield and good *Z* selectivity. Under standard bromination conditions, the hydroxyl group was replaced by Br. With sufficient material in hand, a coupling reaction was used as the third step to build the skipped enyne scaffold. Although previous publications[147] have highlighted the problem of low regioselectivity during the allyl bromide species coupling with ethynyltrimethylsilane (2.5/1 by using CuI, K_2CO_3, Et_4NCl, DMF coupling condition by Rai, 3/1 by using CuI, K_2CO_3, NaI, DMF coupling condition by Trost), as the most straightforward approach it was considered to be worthy of investigation. The TMS-acetylene Grignard reagent and bromoalkene were coupled together successfully using a CuCN catalyzed reaction reported by Zezschwitz.[147b, 147c]According to the author, when (*E*)-bromoalkene was used, only one regioisomer was found in his case, a result which matched that reported in Braddock's paper.[148] A subsequent ^1H NMR study showed that the regioisomers **234** and **235** were formed as a ca.1:1 mixture. It is speculated that the ratio of regioisomers is relatively independent of the coupling conditions but can be significantly affected by the (*E*)/(*Z*) structural difference in the bromoalkenes. All efforts failed when trying to isolate the desired regioisomer **234** from the undesired one **235** and this led to the requirement for the development of another route.



Scheme 13. Synthesis of panaxjapyne A - an initial attempt.

An alternative route was developed (**Scheme 14**) in an attempt to avoid the formation of regioisomers. 1-Iodo-2-decyne **236** was prepared by a standard procedure in high yield using the combination of I_2, PPh_3 and imidazole. The resulting product was combined with ethynyltrimethylsilane in a Sonogashira coupling.[149] By using the procedure reported by Prati et al it was found that compound was formed as a single regioisomer by ^{1}H NMR, and in good yield (74%). The skipped diyne **237** however is unstable and therefore needs to be used freshly or stored in hexane at low temperature.

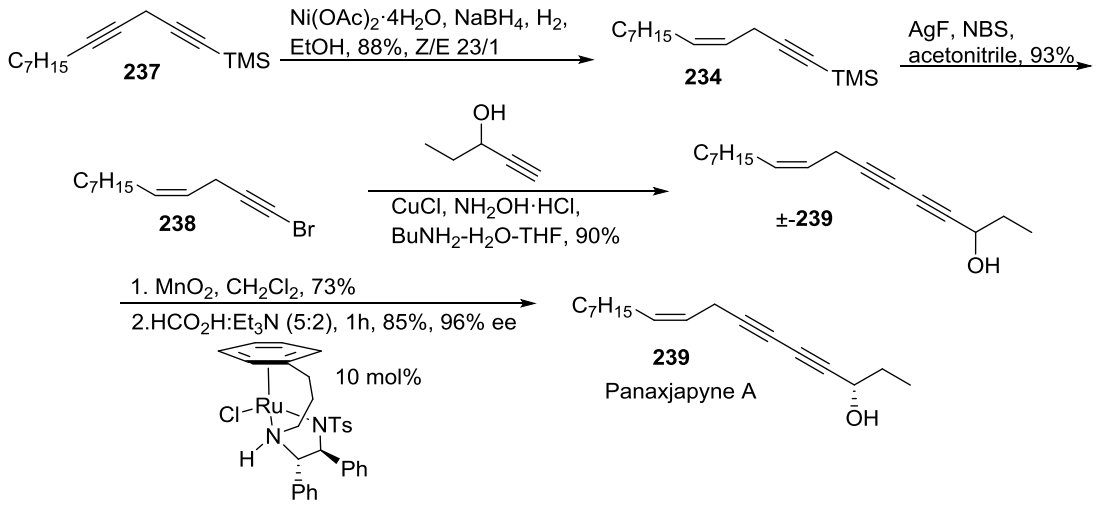


Scheme 14. Synthesis of skipped diyne **237**.

A regio and *Z*-selective hydrogenation using a P-2 Ni catalyst[150] was adopted to prepare (4*Z*)-4-dodecen-1-ynyltrimethylsilane **234** (**Scheme 15**). The reaction is highly regioselective but to achieve the highest yield and *Z*/*E* selectivity it was found that the *in situ* generated P-2 Ni has to be poisoned by ethylenediamine for at least 1.5 h and the reaction must be completed in 1 h. The yield decreased (33%) when the reaction was extended to 3.5 h, probably due to the base sensitivity of the TMS acetylene. The highest *Z*/*E* selectivity measured by ^{1}H NMR was *Z*/*E*=23/1; however, decreasing the poisoning time caused a drop in the *Z*/*E* selectivity. Subsequent AgF and NBS meditated desilylbromination gave the corresponding bromoalkyne **238** in excellent yield (93%).

A highly efficient Cadiot-Chodkiewicz cross-coupling[151] was used to link bromoalkyne **238** and 1-pentyn-3-ol together. Under the conditions modified by Marino,[152] the coupling was completed within 30 min and racemic panaxjapyne A ±-**239** was isolated as the only product. Activated MnO_2 power served as an efficient oxidative reagent to oxidize the propargylic alcohol and was utilized to oxidize the diynols. The MnO_2 oxidation was clean, and when the reaction was finished, only the product **240** spot could be detected by TLC.

At the final stage a very chemo and stereoselective ATH was performed by using 10 mol% of catalyst (*S,S*)-**c2** and the final product panaxjapyne A **239** was isolated in 85% yield and 96% ee (determined after modification see experimental part). The ee value of the synthetic panaxjapyne A was determined using three methods. The ee was shown to be>90% using a modified Mosher ester method and ca. ee 95% by HPLC analysis of racemic panaxjapyne A against the chiral panaxjapyne A. To have better resolution, the enantioselectivity was determined by chiral HPLC to be of 96% ee by analysis of 4-methoxybenzonate derivative of racemic panaxjapyne A and chiral panaxjapyne A.



Scheme 15. Completion of the synthesis of panaxjapyne A.

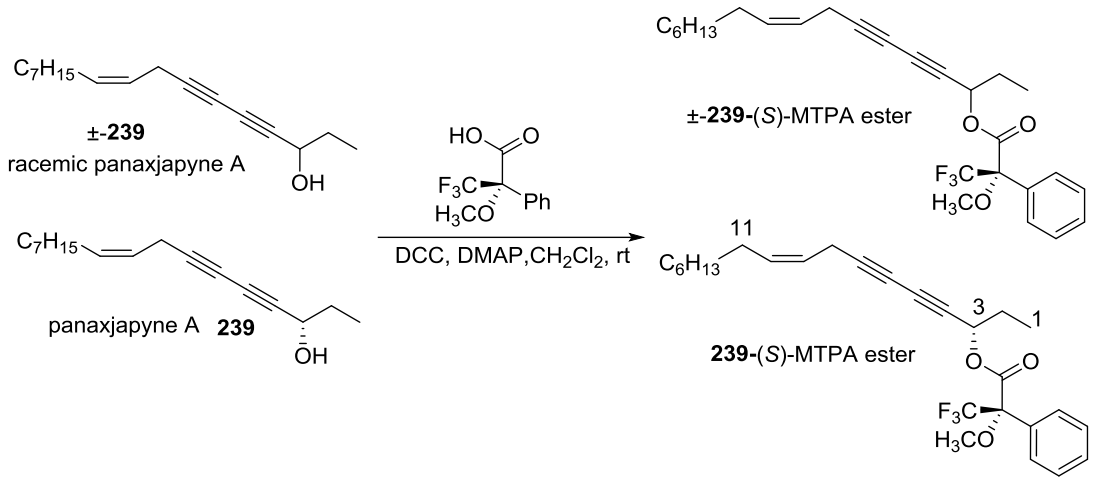
The experimental data for the synthetic panaxjapyne A, including ^{1}H NMR, ^{13}C NMR, optical rotation and Mosher ester were consistent with those reported for the natural panaxjapyne A. The absolute configuration of panaxjapyne A prepared by ATH was assigned to be (*S*) by comparing the natural panaxjapyne A Mosher ester, with racemic and enantio-enriched panaxjapyne A Mosher ester ^{1}H NMR spectra (**Table 24**) of the compounds prepared in this project. (*S*)-Mosher acid was used to synthesize the analytical sample. According to Wu's[99] assignment of natural panaxjapyne A, the chemical shift of (*R*)-MTPA ester minus (*S*)-MTPA ester are: H-1 (-0.026 ppm), H-2 (-0.068 ppm) and H-8 (+0.005 ppm). Based on this chemical shift difference the absolute structure of natural

panaxjapyne A was assigned to be (*S*). Although there are few publications[153] available involving the absolute structure determination of diynols using a modified Mosher ester method, based on the general principal established by Kakisawa,[154] the absolute structure of the synthetic panaxjapyne A prepared herein can be assigned unambiguously (**Table 25**).

Table 24. ^{1}H NMR and ^{13}C NMR of natural panaxjapyne A and synthetic panaxjapyne A.

^{1}H (ppm)	Natural panaxjapyne A	Synthetic panaxjapyne A	^{13}C (ppm)	Natural panaxjapyne A	Synthetic panaxjapyne A
H-1	1.00, t (7.4)	1.01, t (7.4)	C-1	9.3	9.3
H-2	1.72, m	1.79-1.69, m	C-2	30.7	30.7
H-3	4.34,t (6.0)	4.36, q (6.1)	C-3	64.0	64.1
H-8	3.01, d (6.8)	3.03, d (6.9)	C-4	76.7	76.7
H-9	5.49, dt (6.8)	5.55-5.47, m	C-5	69.9	69.9
H-10	5.36, dt (10.4, 7.0)	5.42-5.34, m	C-6	79.5	79.6
H-11	2.01, q (7.0)	2.02, q (7.1)	C-7	64.1	64.1
H-12	1.35, m	1.40-1.22, m	C-8	17.6	17.7
H-13	1.27, m	1.40-1.22, m	C-9	122.0	122.0
H-14	1.27, m	1.40-1.22, m	C-10	133.0	133.0
H-15	1.27, m	1.40-1.22, m	C-11	27.2	27.2
H-16	1.27, m	1.40-1.22, m	C-12	29.2	29.2
H-17	0.99, t (6.6)	0.88, t (7.0)	C-13	29.2	29.2
			C-14	29.2	29.2
			C-15	31.8	31.8
			C-16	22.6	22.7
			C-17	14.1	14.1

1. ^{13}C (125 MHz) and ^{1}H NMR (500 MHz) spectroscopic data reported for natural panaxjapyne A in $CDCl_3$. ^{13}C (100 MHz) and ^{1}H NMR (400 MHz) spectroscopic data for synthetic panaxjapyne A in $CDCl_3$.



Scheme 16. Synthesis of panaxjapyne A (*S*)-MTPA ester.

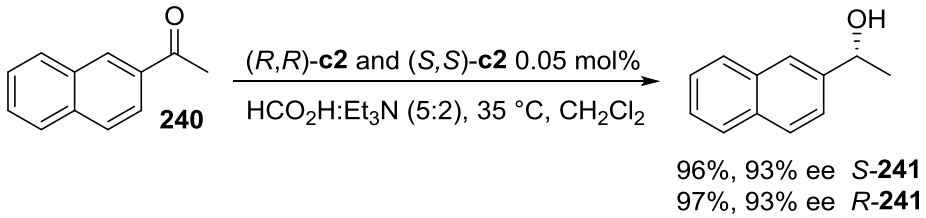
Table 25. ^{1}H NMR Difference between *R* and *S* panaxjapyne A Mosher ester.

H	(*S*)-panaxjapyne A (*S*)-Mosher ester	(±)-panaxjapyne A(*S*)-Mosher ester
H-1	0.93, t, *J* 7.4	0.93, t, *J* 7.4/1.03, t, *J* 7.4
H-2	1.86-1.78, m	1.85-1.78, m/1.92-1.78, m
H-3	5.54, t, *J* 6.4	5.54, t, *J* 5.9/5.51, t, *J* 6.5
OCH_3	3.59, s	3.59, s/3.55, s
H-8	3.04, d, *J* 6.9	3.04, d, *J* 6.5

1. ^{1}H NMR (400 MHz) spectroscopic data for Mosher esters in $CDCl_3$.

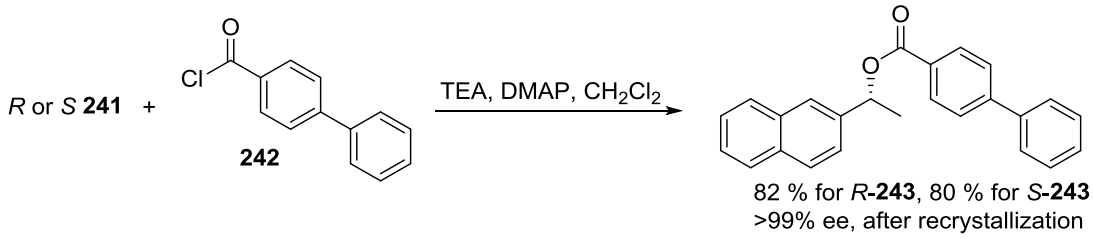
2.4. Synthesis of Chiral 1-(2'-Naphthyl)ethyl-(4-phenylbenzoate) and Scanning Tunnelling Microscopy (STM).

2-Acetonaphthone **240** was reduced independently by (*R*,*R*)-**c2** and (*S*,*S*)-**c2** at 0.05 mol% catalyst loading under standard transfer hydrogenation conditions (**Scheme 17**). The resulting chiral 1-(2'-naphthyl)ethanol (*S*-**241** and *R*-**241**) were formed in similar yields and ee values; 96%, 93% ee from catalyst (*R*,*R*)-**c2** and 97%, 93% ee from (*S*,*S*)-**c2**. The absolute configurations of were determined by comparison of the optical rotations and GC retention times with reported values.[155]



Scheme 17. ATH of 2-acetonaphthone by using catalyst **c2**.

The 93 % ee 1-(2'-naphthyl)ethanol (*S*-**241** and *R*-**241**) were used for esterfication with 4-phenylbenzoyl chloride **242** (**Scheme 18**). Both (*R*) and (*S*) 1-(2'-naphthyl)ethyl-4-phenylbenzoate **243** were formed as solids in satisfactory yields. Simply by a recrystallization from hexane/CH_2Cl_2 (6/1) the ee value was increased to >99 %. The ee values of esters *S*-**243** and *R*-**243** were determined by HPLC. From ^{1}H NMR analysis, the sample after recrystallization is pure enough for the planned scanning tunnelling microscopy imaging experiments.



Scheme 18. Synthesis of chiral 1-(2'-naphthyl)ethyl-4-phenylbenzoate **243**.

Scanning tunnelling microscopy has developed into a useful tool for molecular characterisation over recent years. Specifically, there have been many instances where the chirality of molecules has been inferred from molecular packing or has been imaged unambiguously with the STM. STM can also be used to view the starting materials and products of reactions on surfaces. Considering the imaging of enantio-enriched molecules is an interesting subject chiral compounds *S*-**243** and *R*-**243** were prepared and the behaviours were studied under scanning tunnelling microscopy.

The STM experimentation was carried out on the single crystal surfaces Cu(110) and Au(111) respectively. On the Cu(110) surface at rt, ester was found unable to be imaged due to the copper reduce it to the two corresponding primary alcohols. The proposed mechanism suggests the decomposition based on the dissociative adsorption along the RO-CRO bond to generate the RO(Cu) and RC(Cu)O species which then undergo hydrogenation to generate the alcohols. When was deposited on Cu(110) that holding at -140 °C only 20% of the molecules have fragmented (Figure **83**, picture middle).

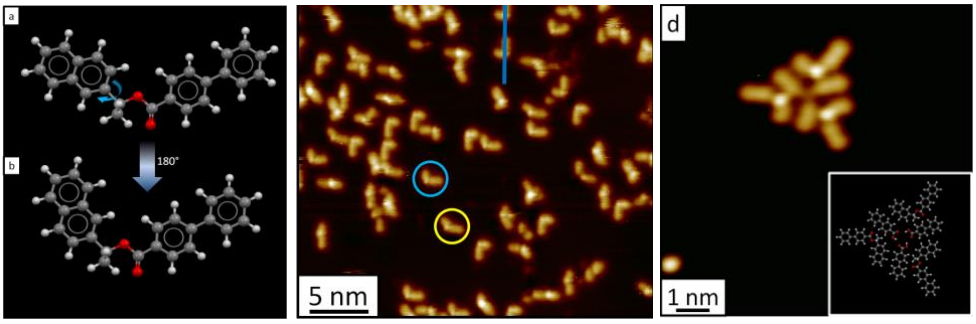


Figure 83. Possible main conformations and STM image.

1. Picture left is computer predicted two possible main conformations of molecule *S*-**243**.
2. Picture middle is the STM image that sample *S*-243 was deposited at -140 °C on Cu(110) surface; the two main conformations were highlighted in this image.
3. Picture right is the STM image that sample *S*-243 was deposited at -196 °C on Au(111) surface;

In contrast to Cu(110), Au(111) did not show any type of dissociation on the surface because it is more inert and (111) as the most compacted therefore less reactive orientation. The ester which contains two structurally distinct extended aromatic ring systems, each of which has the potential to bind to a surface and therefore to 'hold down' the molecule in a predictable conformation with the methyl substituent oriented out of the plane (**Figure 83**, picture right).. On the surface there are two favoured conformations of the ester 90° lobes and 130° lobes (Figure **83**, picture left).

The scanning tunnelling microscopy analysis was carried out by Ben. Moreton under the supervision of Dr Giovanni Costantini. The results from this study were published as part of a collaborative project.[156]

2.5. Conclusions

A group of functionalized aromatic ketones (**98**-**110**, **112** and **113**) were prepared and subjected to asymmetric transfer hydrogenation tests. For this group of compound, high enantioselectivities (up to 99% ee) were found in most of the examples. To demonstrate the use of this transformation, one of the products *R*-**114** was used in the total synthesis of yashabushitriol **129**.

Propargylic α-keto esters (**138**-**140**), β-keto esters (**160**-**162** and **143**, **144**), β-keto thioesters (**141** and **142**), α-methyl-β-keto esters (**163**-**166**), γ-keto esters (**176**-**179**), δ-keto esters (**180**-**183**), 4-pentyne-1,3-diones (**192**-**195**), 1,4-diketones (**197**, **199** and **201**) and 1,5-diketones (**198** and **200**) were prepared and subjected to asymmetric transfer hydrogenation. In general, high ee, dr values and yields were achieved and the behaviour of the different propargylic ketones was fully understood. The method also serves as a key step in the total synthesis of yashabushidiol B **213**.

The first asymmetric transfer hydrogenation of diynones (**223**-**230**) was investigated. In general, high ee values (up to 99% ee) and yields (up to 95% yield) were achieved. The yields were highly dependent on the structures/stabilities of diynones while the ee values were not. ATH of diynones was also used in the total synthesis of panaxjapyne A **239**.

More application including synthesis of highly optically pure ester 1-(2'-naphthyl)ethyl-4-phenylbenzoate **243** (>99% ee) for scanning tunnelling microscopy imaging was described.

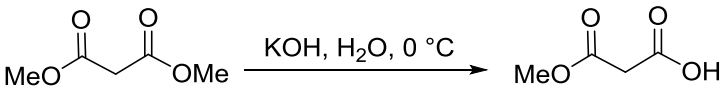
3. Experimental Section.

General Remarks

Unless otherwise stated, all reactions were performed using dry solvents and under an atmosphere of nitrogen. Reactions were monitored by thin layer chromatography (TLC) using silica gel 60 (F254) aluminium plate; visualised using UV_{254} lamp or potassium permanganate dip. NMRs were measured by either a Bruker DPX-300 (300 MHz) or a Bruker DPX-400 (400 MHz). All NMR δ values are in ppm and all *J* values are in Hz. Low resolution mass spectrometry was run on a Bruker Esquire 2000 electrospray mass spectrometer. High resolution mass spectrometry was run on Bruker MicroTOF. Melting points were obtained using a Stuart Scientific Melting Point SMP1 and are uncorrected. Infrared spectroscopy was run on a PerkinElmer Spectrum 100. Optical rotation was obtained from an Optical Activity Ltd. AA-1000 Polarimeter. GC was run on a Hewlett Packard 5890 gas chromatograph linked to a Hewlett Packard HP3396A integrator and column chrompaccyclodextrin-β-236M-19 50 m. HPLC was run on a chromatograph consisting of a Gilson 305 Piston Pump, a Gilson 805 Manometric Module, a Gilson 811B Dynamic Mixer and a Gilson 115 Variable Wavelength Detector linked to a Hewlett Packard 3396 Series II integrator.

3.1. Synthesis of Acid Monoesters and Acid Chloride Monoesters.

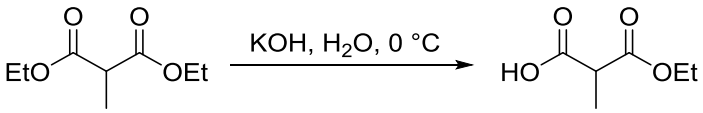
Propanedioic acid, methyl ester 147. This compound is known and has been fully characterized.[157a]



Dimethyl malonate (39.60 g, 299.8mmol), acetonitrile (3 cm^3) and water (25 cm^3) were added together and the mixture was stirred at 0 °C for 30 min. KOH (60 cm^3, 5 M aqueous solution, 0.3 mol) solution was added dropwise within 15 min with vigorous stirring and

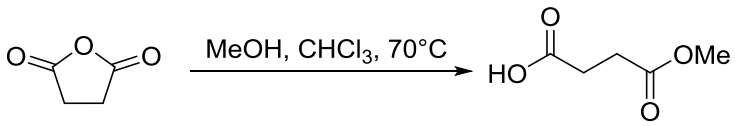
the resulting mixture was stirred for another hour. The mixture was extracted with EtOAc/hexane (2 × 150 cm^3, 1:2 mixture) followed by addition of aqueous HCl (38 cm^3, 12 M solution) and the resulting solution was saturated with NaCl and extracted with EtOAc (4 × 200 cm^3).The combined organic phase was washed with sat NaCl solution (100 cm^3), and dried over sodium sulfate. After vacuum concentration, the crude product was distilled under reduced pressure (88-96 °C, 1-2 bar) to afford pure monomethyl malonate as a colourless oil (25.3 g, 214 mmol, 71%) and a mixture of dimethyl malonate, monomethyl malonate and water as the other fraction (<6% w/w).δ_H (400 MHz, $CDCl_3$) 3.79 (3H, s, CH_3), 3.46 (2H, s, CH_2).

2-Methyl-propanedioic acid, ethyl ester 148. This compound is known and has been fully characterized.[157b]



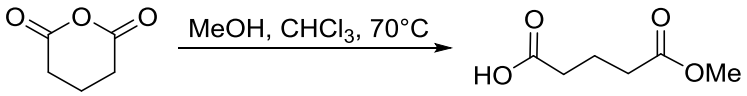
Diethyl methylmalonate (34.8 g, 200 mmol), acetonitrile (3 cm^3) and water (25 cm^3) was added together and the mixture was stirred at 0 °C for 30 min. KOH (60 cm^3, 5 M aqueous solution, 0.3 mol) solution was added dropwise within 15 min with vigorous stirring and the resulting mixture was stirred for another hour. The mixture was extracted with EtOAc/hexane (2 × 150 cm^3, 1:2 mixture) followed by addition of aqueous HCl (24 cm^3,12 M solution) and the resulting solution was saturated with NaCl and extracted with EtOAc (4 × 200 cm^3). The organic phase was washed with sat NaCl solution (100 cm^3), then dried over sodium sulfate. After vacuum concentration, the crude product was distilled under reduced pressure to afford the pure product as a colourless oil (19.9 g, 0.136 mmol, 68 %). δ_H (400 MHz, $CDCl_3$) 4.23 (2H, q, *J* 7.2, $COOCH_2$), 3.48 (1H, q, *J* 7.3, CH), 1.46 (3H, d, *J* 7.3, $CHCH_3$), 1.29 (3H, t, *J* 7.2, CH_2CH_3).

Butanedioic acid, monomethyl ester 149. This compound is known and has been fully characterized.[158]



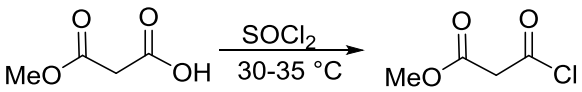
Succinic anhydride (20.0 g, 200 mmol), $CHCl_3$ (30 cm^3) and anhydrous methanol (7.68 g, 240 mmol) were refluxed for 4 h. Solvent and the excess methanol were removed under reduced pressure and the crude product was used without purification. δ_H (400 MHz, $CDCl_3$) 3.71(3H, s, CH_3), 2.72-2.68 (2H, m, CH_2), 2.65-2.62 (2H, m, CH_2).

Pentanedioic acid, monomethyl ester 150. This compound is known and has been fully characterized.[158]



Glutaric anhydride (22.8 g, 200 mmol), $CHCl_3$ (30 cm^3) and anhydrous methanol (7.68 g, 240 mmol) were refluxed for 5 h. Solvent and the excess methanol was removed under reduced pressure and the crude product was used without further purification. δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, CH_3), 2.47-2.39 (4H, m, CH_2CO), 2.00-1.93 (2H, m, CH_2).

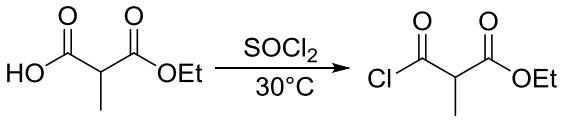
3-Chloro-3-oxo-propanoic acid, methyl ester 151. This compound is known and has been fully characterized.[159]



Propanedioic acid, monomethyl ester (2.36 g, 20.0 mmol) and $SOCl_2$ (4.76 g, 2.92 cm^3, 40.0 mmol) were warmed to 30-35 °C for 18 h. The excess thionyl chloride was removed and the crude product was distilled into a collecting flask cooled by a dry ice/acetone bath

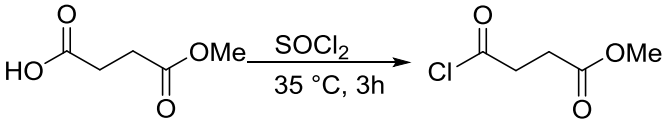
to afford product **151** (20-24 °C, 1 mm Hg) as colourless liquid (2.33 g, 17.1 mmol, 85%). δ_H (400 MHz, $CDCl_3$) 3.86 (2H, s, CH_2), 3.79 (3H, s, $COOCH_3$).

2-Methyl 3-chloro-3-oxo-propanoic acid, ethyl ester 152. This compound is known and has been fully characterized.[159]



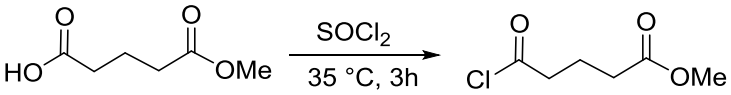
Propanedioic acid, 2-methyl-1-ethyl ester (2.92 g, 20.0 mmol) and $SOCl_2$ (4.76 g, 2.92 cm^3, 40.0 mmol) were warmed to 30 °C for 20 h. The excess thionyl chloride was removed and the crude product was distilled into a collecting flask cooled by a dry ice/acetone bath to afford product **152** (38-40 °C, 1 mm Hg) as a colourless liquid (2.65 g, 16 mmol, 80%). δ_H (400 MHz, $CDCl_3$) 4.19(2H, qd, *J* 7.1 2.8, $COOCH_2$), 3.78 (1H, q, *J* 7.2, CH), 1.46 (3H, d, *J* 7.2, $CHCH_3$), 1.24 (3H, t, *J* 7.1, CH_3).

4-Chloro-4-oxo-butanoic acid, methyl ester 153. This compound is known and has been fully characterized.[160]



Butanedioic acid, monomethyl ester (23.1 g, 200 mmol) and $SOCl_2$ (47.2 g, 29.2 cm^3, 400 mmol) was warmed to 35 °C for 3 h. The excess thionyl chloride was removed and the crude product was distilled into a collecting flask cooled by a dry ice/acetone bath to afford product **153** (38-40 °C, 1 mm Hg) as a colourless liquid (24.35 g, 161.8 mmol, 82%). δ_H (400 MHz, $CDCl_3$) 3.72(3H, s, $COOCH_3$) 3.23 (2H, t, *J* 6.7, CH_2), 2.69 (2H, t, *J* 6.7, CH_2).

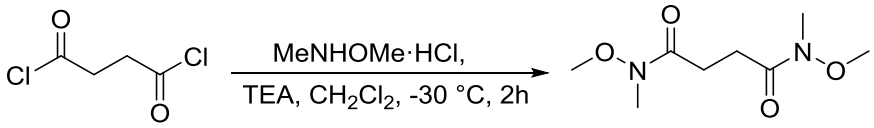
5-Chloro-5-oxo-pentanoic acid, methyl ester 154. This compound is known and has been fully characterized.[160]



Pentanedioic acid, monomethyl ester (13.2 g, 100 mmol) and $SOCl_2$ (23.6 g, 14.6 cm^3, 200mmol) was wormed to 35 °C for 3 h. The excess thionyl chloride was removed and the crude product was distilled into a collecting flask cooled by a dry ice/acetone bath to afford product **154** (49-52 °C, 1 mm Hg) as a colourless liquid (14.81g, 90.0 nmol, 90%). δ_H (400 MHz, $CDCl_3$) 3.67 (3H, s, $COOCH_3$) 2.98 (2H, t, *J* 7.1, CH_2), 2.29 (2H, t, *J* 7.1, CH_2), 1.99-1.90 (2H, m, CH_2).

3.2. Synthesis of Weinreb Diamides.

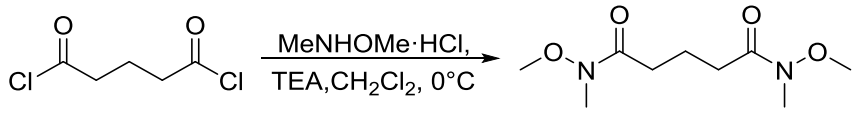
***N,N'*-Dimethoxy-*N,N'*-dimethylsuccinamide 155.** This compound is known and has been fully characterized.[161]



Triethylamine (1.44 g, 14.3 mmol) was added to a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (720 mg, 7.38 mmol) in CH_2Cl_2 (30 cm^3) and the solution was cooled to -30 °C, succinyl chloride (545 mg, 3.52 mmol) in CH_2Cl_2 (3 cm^3) was added dropwise. After 2 h, the solution was allowed to warm up to room temperature for another 1 h and quenched with saturated aqueous $NaHCO_3$ (10 cm^3). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic extracts were washed with brine (5 cm^3) and dried over $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent CH_2Cl_2) to give pure

product **155** (684 mg, 3.35 mmol, 95%) as a white solid. δ_H (400 MHz, $CDCl_3$) 3.74 (6H, s, 2 × OCH_3), 3.19 (6H, s, 2 × CH_3), 2.78 (4H, s, 2 × CH_2).

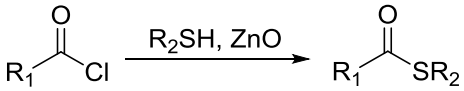
***N,N'*-Dimethoxy-*N,N'*-dimethylglutaramide 156.** This compound is known and has been fully characterized.[161]



Triethylamine (1.43 g, 14.3 mmol) was added to a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (720 mg, 7.38 mmol) in CH_2Cl_2 (30 cm^3) and the solution was cooled to 0 °C. Glutaryl chloride (591 mg, 3.50 mmol) in CH_2Cl_2 (5 cm^3) was then added dropwise. After 2 h, the solution was allowed to warm up to room temperature overnight and quenched with saturated aqueous $NaHCO_3$ (10 cm^3). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic extracts were washed with brine (5 cm^3) and dried over $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent CH_2Cl_2/EtOAc=2:1) to afford the pure Weinreb diamide **156** (700 mg, 3.2 mmol, 92%) as a brown oil. δ_H (400 MHz, $CDCl_3$) 3.61 (6H, s, 2 × OCH_3), 3.11 (6H, s, 2 × CH_3), 2.45 (4H, t, *J* 7.1, 2 × $COCH_2$), 1.91 (2H, p, *J* 7.1, CH_2).

3.3 Synthesis of Thioesters.

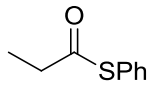
General Procedure



To a stirred mixture of acid chloride (1 mmol) and thiol (1 mmol), zinc oxide powder (0.5 mmol, variable) was added carefully at rt. Stirring was continued for 1 h and CH_2Cl_2 (10

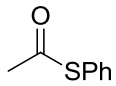
mL) was added, zinc oxide was filtered off and washed with more CH_2Cl_2 (20 cm^3). The combined organic phase was washed with sat $NaHCO_3$ (5 cm^3), brine (5 cm^3) and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure furnished product pure enough for next step.

S-Phenyl thiopropionate 157. This compound is known and has been fully characterized.[162]



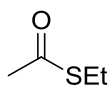
This compound was prepared following the general procedure above using propionyl chloride (1.85 g, 20.0 mmol), thiophenol (2.20 g, 20.0 mmol) and zinc oxide (0.82 g, 10.0 mmol). The product **157** was isolated as described above as a colourless oil (2.86 g, 17.2 mmol, 86%). δ_H (400 MHz, $CDCl_3$) 7.42-7.38 (5H, m, Ph), 2.68 (2H, q, *J* 7.5, CH_2), 1.23 (3H, t, *J* 7.5, CH_3).

S-Phenyl thioacetate 158. This compound is known and has been fully characterized. [162]



This compound was prepared following the general procedure above using acetyl chloride (7.85 g, 100 mmol), thiophenol (11.0 g, 100 mmol) and zinc oxide (2.0 g, 24.6 mmol). The product **158** was isolated as described above as a colourless oil (13.90 g, 91.4 mmol, 92%). δ_H (400 MHz, $CDCl_3$) 7.43-7.38 (5H, m, Ph), 2.41 (3H, s, CH_3).

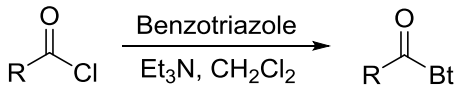
S-Ethyl thioacetate 159. This compound is known and has been fully characterized. [162]



This compound was prepared following the general procedure above using acetyl chloride (4.40 g, 56.0 mmol), ethylthiol (3.31 g, 53.4 mmol) and zinc oxide (2.20 g, 27.0 mmol). The product **159** was isolated as described above as a colourless oil (4.68 g, 44.9 mmol, 84%). δ_H (400 MHz, $CDCl_3$) 2.87 (2H, q, *J* 7.4, CH_2), 2.32 (3H, s, CH_3), 1.25 (3H, t, *J* 7.4, $CH_2C\mathit{H}_3$).

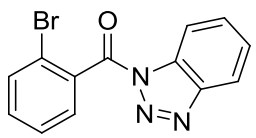
3.4. Synthesis of N-Acylbenzotriazoles.

General Procedure [1]



Benzotriazole (5.95 g, 50.0 mmol) in dichloromethane (100 cm^3) was cooled to 0 °C and triethylamine (9.0 cm^3, 60.0 mmol) was added, followed by addition of the acid chloride (55.0 mmol). The mixture was stirred at room temperature for 30 min then HCl (2 M, 50 cm^3) was added to the mixture. The aqueous phase was extracted with dichloromethane once (50 cm^3) and the combined organic phase was washed with sat Na_2CO_3 (2 × 30 cm^3), brine (30 cm^3) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the product was dried under vacuum before use.

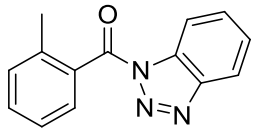
1-*o*-Bromobenzoylbenzotriazole 83. This compound is novel.



This compound was prepared following the general procedure above using benzotriazole (1.19 g, 10.0 mmol), triethylamine (1.8 cm^3, 12.0 mmol) and *o*-bromobenzoyl chloride (2.4 g, 11.0 mmol). The product was isolated as described above as light yellow crystals (2.9 g, 9.6 mmol, 96%). MP 59 °C; (found (ESI): M^+ + Na, 323.9743. $C_{13}H_8N_3O^{79}Br$

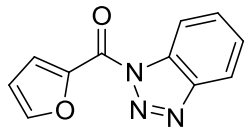
requires M, 323.9748); ν_{max} 1721, 1355, 1285, 1046, 1031, 934, 885, 744, 732, 686 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.42 (1H, d, *J* 8.3, Ar), 8.06 (1H, d, *J* 8.3, Ar), 7.77-7.72 (2H, m, Ar), 7.65-7.45 (4H, m, Ar); δ_C (75 MHz, $CDCl_3$) 166.5, 146.3, 135.1, 133.3, 132.6, 131.3, 130.8, 130.1, 127.3, 126.7, 120.6, 120.4, 114.5; *m/z* (EI-MS) 323.9 $(M+Na)^+$.

1-o-Toluoylbenzotriazole 84. This compound is known but not fully characterized.[163]



This compound was prepared following the general procedure above using benzotriazole (3.96 g, 33.0 mmol), triethylamine (6.0 cm^3, 39.6 mmol) and *o*-toluoyl chloride (5.6 g, 36.3 mmol). The product was isolated as described above as white crystals (7.8 g, 33 mmol, 99%). MP 112 °C; (found (ESI): M^+ + Na, 260.0794. $C_{14}H_{11}N_3O$ requires M, 260.0799); ν_{max} 1703, 1358, 1286, 1045, 933, 889, 750, 729 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.40 (1H, d, *J* 8.1, Ar), 8.15 (1H, d, *J* 8.1, Ar), 7.71 (1H, t, *J* 7.3, Ar), 7.64 (1H, d, *J* 7.3, Ar), 7.58-7.49 (2H, m, Ar), 7.38-7.33 (2H, m, Ar), 2.42 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 167.7, 145.5, 137.4, 131.7, 131.3, 131.2, 130.5, 129.8, 129.5, 125.8, 124.9, 119.7, 114.0, 19.5; *m/z* (EI-MS) 260.1 $(M+Na)^+$.

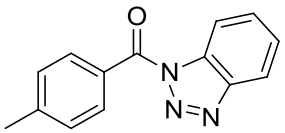
1-(2-Furanylcarbonyl)benzotriazole 85. This compound is known and has been fully characterized.[164]



This compound was prepared following the general procedure above using benzotriazole (3.96 g, 33.0 mmol), triethylamine (6.0 cm^3, 39.6 mmol) and 2-furoyl chloride (4.7 g, 36.3 mmol). The product was isolated as described above as white crystals (7.1 g, 33 mmol,

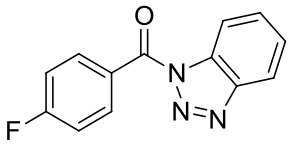
99%). δ_H (300 MHz, $CDCl_3$) 8.42 (1H, d, *J* 8.3, Ar), 8.19-8.15 (2H, m, Ar), 7.88 (1H, d, *J* 1.7, Ar), 7.73-7.68 (1H, m, Ar), 7.58-7.53 (1H, m, Ar), 6.74 (1H, dd, *J* 3.7, 1.7, Ar); δ_C (75 MHz, $CDCl_3$) 155.0, 149.0, 145.6, 144.6, 132.1, 130.5, 126,4, 124.8, 120.2, 114.7, 130.0; *m/z* (EI-MS) 236.1 $(M+Na)^+$.

1-*p*-Toluoylbenzotriazole 86. This compound is known and has been fully characterized.[164]



This compound was prepared following the general procedure above using benzotriazole (2.00 g, 16.5 mmol), triethylamine (3.0 cm^3, 19.8 mmol) and *p*-toluoyl chloride (2.8 g, 18.2 mmol). The product was isolated as described above as white crystals (3.9 g, 16.4 mmol, 99%). δ_H (300 MHz, $CDCl_3$) 8.37 (1H, d, *J* 8.1, Ar), 8.17 (1H, d, masked, Ar), 8.14 (2H, d, *J* 7.8, Ar), 7.70 (1H, dd, *J* 7.7, 7.5, Ar), 7.54 (1H, d, *J* 8.1, 7.5, Ar), 7.38 (2H, d, *J* 7.8, Ar), 2.50 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 166.6, 144.9, 132.4, 131.9, 130.3, 129.2, 128.6, 126.2, 124.8, 120.1, 114.8, 21.8; *m/z* (EI-MS) 260.1 $(M+Na)^+$.

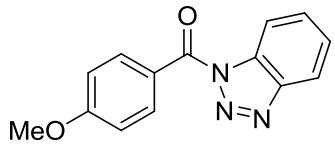
1-*p*-Fluorobenzoylbenzotriazole 87. This compound is novel.



This compound was prepared following the general procedure above using benzotriazole (3.64 g, 30.6 mmol), triethylamine (5.5 cm^3, 36.7 mmol) and *p*-fluorobenzoyl chloride (5.34 g, 33.6 mmol). The product was isolated as described above as white crystals (8.0 g, 29 mmol, 96%). MP 118 °C; (found (ESI): M^+ + Na, 264.0544. $C_{13}H_8FN_3O$ requires M,

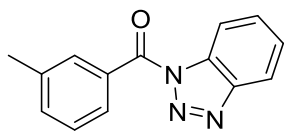
264.0549); ν_{max} 1708, 1366, 1288, 1228, 1039, 935, 845, 748 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.35 (1H, d, *J* 8.2, Ar), 8.31-8.27 (2H, m, Ar), 8.14 (1H, d, *J* 8.2, Ar), 7.71-7.66 (1H, m, Ar), 7.56-7.51 (1H, m, Ar), 7.27-7.21 (2H, m, Ar); δ_C (75 MHz, $CDCl_3$) 167.2, 164.7, 163.8, 134.0 (d, *J* 9.5), 131.7, 129.9, 127.0, 125.8, 119.6, 115.2, 114.2 (d, *J* 22.1); *m/z* (EI-MS) 264.1 $(M+Na)^+$.

1-*p*-Methoxylbenzoylbenzotriazole 88. This compound is known and has been fully characterized.[165]



This compound was prepared following the general procedure above using benzotriazole (4.77 g, 40.1 mmol), triethylamine (7.2 cm^3, 48.1 mmol) and *p*-methoxylbenzoyl chloride (7.52 g, 44.1 mmol). The product was isolated as described above as white crystals (10.1 g, 40 mmol, 99%). δ_H (300 MHz, $CDCl_3$) 8.35 (1H, d, *J* 8.3, Ar), 8.29 (2H, d, *J* 9.0, Ar), 8.15 (1H, d, *J* 8.2, Ar), 7.67 (1H, dd, *J* 8.3, 7.2, Ar), 7.52 (1H, d, *J* 8.2, 7.2, Ar), 7.06 (2H, d, *J* 9.0, Ar), 3.92 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 165.0, 163.6, 145.0, 133.8, 131.9, 129.5, 125.5, 122.8, 119.5, 114.2, 113.3, 55.0; *m/z* (EI-MS) 276.1 $(M+Na)^+$.

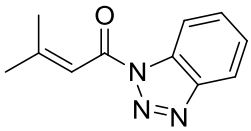
1-*m*-Toluoylbenzotriazole 89. This compound is known but not fully characterized.[166]



This compound was prepared following the general procedure above using benzotriazole (2.00 g, 16.5 mmol), triethylamine (3.0 cm^3, 19.8 mmol) and *m*-toluoyl chloride (2.8 g, 18.2 mmol). The product was isolated as described above as white crystals (3.9 g, 16.4

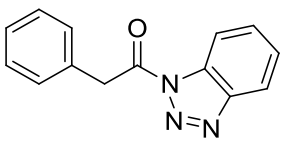
mmol, 99%). MP 65 °C; (found (ESI): M^+ + Na, 260.0794. $C_{14}H_{11}N_3O_4$ requires M, 260.0799); ν_{max} 1701, 1364, 1289,1153, 1044, 950, 748, 730 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.36 (1H, d, *J* 8.3, Ar), 8.15 (1H, d, *J* 8.3, Ar), 8.01-7.99 (2H, m, Ar), 7.68 (1H, t, *J* 8.0, Ar), 7.55-7.43 (3H, m, Ar), 2.46 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 166.9, 145.8, 138.3, 134.5, 132.4, 132.1, 131.5, 130.3, 129.0, 128.3, 126.3, 120.1, 114.8, 21.4; *m/z* (EI-MS) 260.1 $(M+Na)^+$.

1-(3-Methyl-1-oxo-2-butenyl)-benzotriazole 90. This compound is known and has been fully characterized.[167]



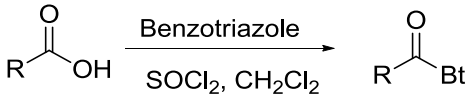
This compound was prepared following the general procedure above using benzotriazole (2.00 g, 16.5 mmol), triethylamine (3.0 cm^3, 19.8 mmol) and 3,3-dimethylacryloyl chloride (2.16 g, 18.2 mmol). The product was isolated as described above as a white solid (3.1 g, 15.3 mmol, 93%). δ_H (300 MHz, $CDCl_3$) 8.36 (1H, d, *J* 8.3, Ar), 8.15 (1H, d, *J* 8.3, Ar), 8.01-7.99 (2H, m, Ar), 7.68 (1H, t, *J* 8.0, Ar), 7.55-7.43 (3H, m, Ar), 2.46 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 164.4, 163.4, 146.2, 131.6, 129.9, 125.8, 120.0, 118.2, 114.8, 28.6, 21.7.

1-(1H-benzotriazol-1-yl)-2-phenyl-ethanone 94. This compound is known and has been fully characterized.[168]



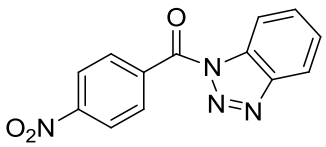
This compound was prepared following the general procedure above using benzotriazole (2.98 g, 25.0 mmol), triethylamine (4.5 cm^3, 30.0 mmol) and phenylacetyl chloride (4.25 g, 27.5 mmol). The product was isolated as described above as a white solid (5.90 g, 25.0 mmol, 99%). δ_H (300 MHz, $CDCl_3$) 8.24 (1H, d, *J* 8.3, Ar), 8.10 (1H, d, *J* 8.3, Ar), 7.61 (1H, t, *J* 8.1, Ar), 7.50-7.45 (3H, m, Ar), 7.39-7.30 (3H, m, Ar), 4.72 (2H, s, CH_2); δ_C (75 MHz, $CDCl_3$) 170.3, 146.3, 132.5, 131.3, 130.5, 129.9, 128.9, 127.7, 126.3, 120.2, 114.5, 42.1; *m/z* (EI-MS) 260.1 $(M+Na)^+$.

General Procedure [2]



Benzotriazole (1.19 g, 10.0 mmol) in dichloromethane (13 cm^3) was cooled to 0 °C then $SOCl_2$ (0.19 cm^3, 2.5 mmol) was added dropwise. The mixture was stirred at room temperature for 30 min then acid (0.42 g, 2.5 mmol) in CH_2Cl_2 (10 cm^3) was added. The mixture was stirred at rt for 3 h, the precipitate was removed by filtration and rinsed with more CH_2Cl_2. The filtrate was washed with NaOH solution (2 M, 2 × 10 cm^3), brine (10 cm^3) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product was dried under vacuum before use.

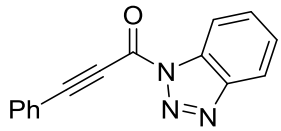
1-*p*-Nitrobenzoylbenzotriazole 97. This compound is known and has been fully characterized.[164]



This compound was prepared following the general procedure above using benzotriazole (1.19 g, 10.0 mmol), $SOCl_2$ (0.19 cm^3, 2.5 mmol) and *p*-nitrobenzoyl acid (0.42 g, 2.5 mmol). The product was isolated as white crystals (0.54 g, 2.0 mmol, 81%). δ_H (300 MHz,

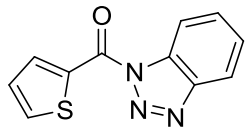
$CDCl_3$) 8.45-8.38 (5H, m, Ar), 8.20 (1H, d, *J* 8.3, Ar), 7.77 (1H, d, *J* 7.2, Ar), 7.61 (1H, d, *J* 7.2, Ar); δ_C (75 MHz, $CDCl_3$) 164.1, 145.0, 136.3, 135.9, 132.0, 130.4, 126.4, 122.9, 120.7, 119.9, 114.

1-(3-Phenyl-1-oxo-2-propynyl)-benzotriazole 95. This compound is known and has been fully characterized.[169]



This compound was prepared following the general procedure above using benzotriazole (2.38 g, 20.0 mmol), $SOCl_2$ (0.38 cm^3, 5.0 mmol) and propiolic acid (0.73 g, 5.0 mmol). The product was isolated as a white solid (1.16 g, 0.47 mmol, 93%). δ_H (300 MHz, $CDCl_3$) 8.29 (1H, d, *J* 8.2, Ar), 8.14 (1H, d, *J* 8.3, Ar), 7.80-7.76 (2H, m, Ar), 7.67 (1H, t, *J* 7.7 Ar), 7.56-7.50 (2H, m, Ar), 7.46-7.42 (2H, m, Ar); δ_C (75 MHz, $CDCl_3$) 150.4, 146.3, 133.7, 131.7, 130.9, 130.6, 128.8, 126.6, 120.4, 119.0, 114.3, 96.0, 81.3; *m/z* (EI-MS) 270.1 $(M+Na)^+$.

1-(2-Thienylcarbonyl)-benzotriazole 96. This compound is known and has been fully characterized.[168]

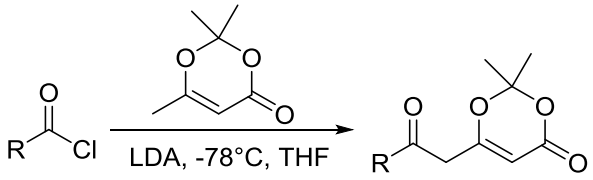


This compound was prepared following the general procedure above using benzotriazole (9.52 g, 80.0 mmol), $SOCl_2$ (1.52 cm^3, 20.0 mmol) and 2-thiophenecarboxylic acid (2.56 g, 20.0 mmol). The product was isolated as white solid (3.60 g, 15.7 mmol, 79%). δ_H (300 MHz, $CDCl_3$) 8.56 (1H, dd, *J* 4.0, 1.3, Ar), 8.15 (1H, d, *J* 8.3, Ar), 7.87 (1H, dd, *J* 4.0, 1.3,

Ar), 7.67 (1H, t, *J* 8.2, Ar), 7.53 (1H, t, *J* 8.2, Ar), 7.27 (1H, t, *J*4.0, Ar); δ_C (75 MHz, $CDCl_3$) 159.3, 145.8, 138.5, 137.3, 133.4, 132.2, 130.5, 128.1, 126.4, 120.3, 114.9; *m/z* (EI-MS) 252.0 $(M+Na)^+$.

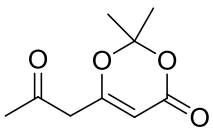
3.5. Synthesis of 2,2-Dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-ones.

General Procedure [1]



To a solution of diisopropylamine (6.2 g, 60 mmol) in THF (100 cm^3) at –78 °C was added *n*-BuLi (1.6 M in hexane, 41.2 cm^3, 66 mmol) dropwise over 20 min then a solution of 2,2,6-trimethyl-1,3-dioxin-4-one (7.04 g, 49.6 mmol) in THF (50 cm^3) was added dropwise over 20 min. After stirring for 1.5 h, the acid chloride (33 mmol) was added in one portion. The resulting mixture was stirred at –78 °C for 30 min and sat NH_4Cl (100 cm^3) was added. The mixture was extracted with ethyl acetate (3 × 60 cm^3) and the combined organic phase was washed with brine (50 cm^3) and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=8:1-4:1).

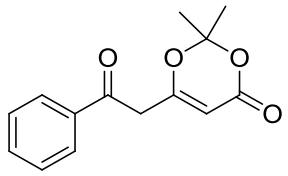
2,2-Dimethyl-6-(2-oxo-2-methylethyl)-4H-1,3-dioxin-4-one 98. This compound is known and has been fully characterized.[170]



This compound was prepared following the general procedure above using diisopropylamine (0.77 g, 7.5 mmol), *n*-BuLi (1.6 cm^3, 7.0 mmol), 2,2,6-trimethyl-1,3-

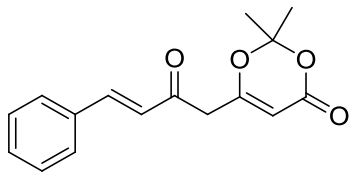
dioxin-4-one (0.88 g, 6.2 mmol) and acetyl chloride (0.44 g, 5.1 mmol). The product was isolated as described above as a colourless oil (0.15 g, 0.8 mmol, 15%). (found (ESI): M^+ + Na, 207.0625. $C_9H_{12}O_4$ requires M, 207.0633); δ_H (300 MHz, $CDCl_3$) 5.35 (1H, s, =CH), 3.37 (2H, s, CH_2), 2.25, (3H, s, $COCH_3$), 1.72 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 200.9, 164.4, 160.7, 107.2, 96.6, 47.9, 30.2, 25.0; *m/z* (EI-MS) 207.1 $(M+Na)^+$.

2,2-Dimethyl-6-(2-oxo-2-phenylethyl)-4H-1,3-dioxin-4-one 99. This compound is known and has been fully characterized.[171]



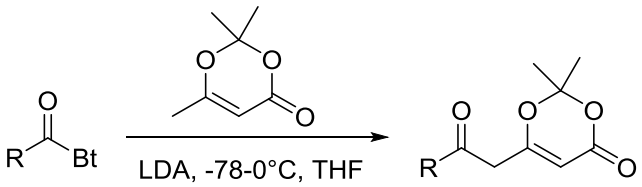
This compound was prepared following the general procedure above using diisopropylamine (0.77 g, 7.5 mmol), *n*-BuLi (1.6 cm^3, 7.0 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (0.88 g, 6.2 mmol) and benzoyl chloride (0.82 g, 5.8 mmol). The product was isolated as described above as a light yellow solid (0.40 g, 1.6 mmol, 26%). (found (ESI): M+ + Na, 269.0789. $C_9H_{12}O_4$ requires M, 269.0784); ν_{max} 1715, 1683, 1639, 1390, 1375, 1329, 1271, 1219, 1188, 1016, 820, 762, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.94 (2H, d, J 7.7, Ph), 7.65-7.61 (1H, m, Ph), 7.53-7.49 (2H, m, Ph), 5.43 (1H, s, =CH), 3.90 (2H, s, CH2), 1.70 (6H, s, 2 × CH3); δ_C (75 MHz, $CDCl_3$) 192.5, 164.6, 160.1, 135.2, 133.4, 128.3, 127.7, 106.7, 96.4, 42.7, 24.4; *m/z* (EI-MS) 269.1 $(M+Na)^+$.

2,2-Dimethyl-6-[(3*E*)-2-oxo-4-phenyl-3-buten-1-yl]-4H-1,3-dioxin-4-one 100. This compound is known and has been fully characterized.[171a]



This compound was prepared following the general procedure above using diisopropylamine (5.35 g, 7.5 mmol), *n*-BuLi (31 cm^3, 49.5 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (5.3 g, 37.5 mmol) and *trans*-cinnamoyl chloride (5.7 g, 34.8 mmol) and the product was isolated as described above as colourless crystals (1.23 g, 4.5 mmol, 13%). (found (ESI): M^+ + Na, 273.1121. $C_{16}H_{17}O_4$ requires M, 273.1126); ν_{max} 1726, 1663, 1626, 1368, 1182, 1015, 979, 805, 744, 687 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (1H, d, *J* 16.1, PhC*H*=C), 7.57-7.55 (2H, m, Ph), 7.47-7.40 (3H, m, Ph), 6.77 (1H, d, *J* 16.1, PhCH=C*H*), 5.43 (1H, s, =CHCOO), 3.59 (2H, s, CH_2), 1.72 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 191.8, 164.3, 164.1, 144.3, 133.2, 130.6, 128.5, 127.9, 124.0, 106.6, 96.2, 44.8, 22.4; *m/z* (EI-MS) 273.1 $(M+Na)^+$.

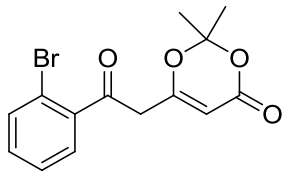
General Procedure [2]



To a solution of diisopropylamine (6.2 g, 60 mmol) in THF (100 cm^3) at –78 °C was added *n*-BuLi (1.6 M in hexane, 41.2 cm^3, 66 mmol) dropwise over 20 min then a solution of 2,2,6-trimethyl-1,3-dioxin-4-one (7.04 g, 49.6 mmol) in THF (50 cm^3) was added dropwise over 20 min. After stirring for 1.5 h, a solution of 1-acylbenzotriazole (43 mmol) in THF (40 cm^3) was added in one portion. The resulting mixture was stirred at –78 °C for 3 h and allowed to warm to room temperature overnight. Sat NH_4Cl (10 cm^3) was added to quench the reaction, and water (200 cm^3) was added. The mixture was extracted with

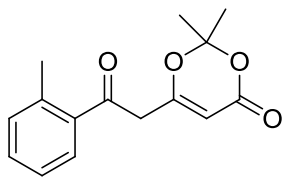
ethyl acetate (3 × 60 cm^3). The combined organic phase was washed with Na_2CO_3 (2 × 50 cm^3), brine (50 cm^3), dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=8:1-4:1).

2,2-Dimethyl-6-(2-oxo-2-*o*-bromo-phenylethyl)-4H-1,3-dioxin-4-one 101. This compound is novel.



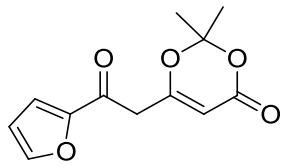
This compound was prepared following the general procedure above using diisopropylamine (6.0 g, 6.0 mmol), *n*-BuLi (4.0 cm^3, 6.3 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (0.69 g, 4.8 mmol) and 1-*o*-bromobenzoylbenzotriazole (1.23 g, 4.1 mmol) and the product was isolated as described above as a yellow oil (0.28 g, 0.86 mmol, 21%). (found (ESI): M^+ + Na, 346.9889. $C_{14}H_{13}O_4{}^{79}Br$ requires M, 346.9894); ν_{max} 1709, 1634, 1390, 1373, 1272, 1251, 1200, 1015, 751 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (1H, dd, *J* 7.6, 1.4, Ar), 7.17-7.11 (3H, m, Ar), 5.44 (1H, s, =CH), 3.90 (2H, s, CH_2), 1.65 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 196.5, 164.4, 161.0, 139.8, 134.1, 132.7, 129.2, 127.7, 119.1, 107.4, 96.9, 46.7, 24.9; *m/z* (EI-MS) 347.0 $(M+Na)^+$.

2,2-Dimethyl-6-(2-oxo-2-o-methyl-phenylethyl)-4H-1,3-dioxin-4-one 102. This compound is novel.



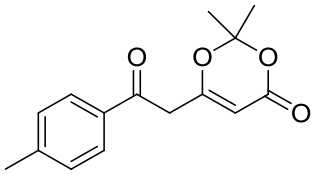
This compound was prepared following the general procedure above using diisopropylamine (0.75 g, 7.5 mmol), *n*-BuLi (5.1 cm^3, 8.3 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (0.85 g, 5.7 mmol) and 1-*o*-toluoylbenzotriazole (1.18 g, 5.0 mmol) and the product was isolated as described above as a light yellow solid (0.39 g, 1.5 mmol, 30%). MP 84 °C; (found (ESI): M^+ + Na, 283.0941. $C_{15}H_{16}O_4$ requires M, 283.0946); ν_{max} 1723, 1681, 1636, 1374, 1272, 1201, 1015, 761 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.59 (1H, d, *J* 7.5, Ar), 7.37 (1H, t, *J* 7.5, Ar), 7.27-7.22 (2H, m, Ar), 5.34 (1H, s, =CH), 3.79 (2H, s, CH_2), 2.46 (3H, s, CH_3), 1.59 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 196.1, 165.3, 160.8, 139.1, 136.2, 132.4, 129.0, 125.9, 107.2, 96.8, 45.9, 24.9, 21.4; *m/z* (EI-MS) 283.1 $(M+Na)^+$.

2,2-Dimethyl-6-[2-(2-furanyl)-2-oxoethyl]-4H-1,3-dioxin-4-one 103. This compound is known and has been fully characterized.[171a]



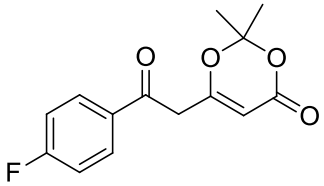
This compound was prepared following the general procedure above using diisopropylamine (0.60 g, 6.0 mmol), *n*-BuLi (4.0 cm^3, 6.3 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (0.69 g, 4.8 mmol) and 1-(2-furanylcarbonyl)benzotriazole (0.87 g, 4.1 mmol) and the product was isolated as described above as a dark brown solid (0.27 g, 1.1 mmol, 27%). (found (ESI): M^+ + Na, 237.0757. $C_{12}H_{13}O_5$ requires M, 237.0763); ν_{max} 1715, 1670, 1640, 1463, 1389, 1373, 1271, 1247, 1200, 1191, 1155, 1014, 778 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (1H, d, *J* 1.7, Ar), 7.29 (1H, d, *J* 3.6, Ar), 6.60 (1H, dd, *J* 3.6, 1.7, Ar), 5.46 (1H, s, =CH), 3.78 (2H, s, CH_2), 1.70 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 192.5, 164.6, 160.1, 135.2, 133.4, 128.3, 127.7, 106.7, 96.4, 42.7, 24.4; *m/z* (EI-MS) 259.0 $(M+Na)^+$.

2,2-Dimethyl-6-(2-oxo-2-*p*-methyl-phenylethyl)-4H-1,3-dioxin-4-one 104. This compound is known and has been fully characterized.[171a]



This compound was prepared following the general procedure above using diisopropylamine (1.5 g, 15 mmol), *n*-BuLi (10.3 cm^3, 16.5 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (1.7 g, 11.4 mmol) and 1-*p*-toluoylbenzotriazole (2.37 g, 10.0 mmol) and the product was isolated as described above as a light yellow solid (1.2 g, 4.6 mmol, 46%). (found (ESI): M^+ + Na, 283.0941. $C_{15}H_{16}O_4$ requires M, 283.0946); ν_{max} 1725, 1683, 1605, 1373, 1200, 1013, 828, 804 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.2, Ar), 7.30 (2H, d, *J* 8.2, Ar), 5.41 (1H, s, =CH), 3.88 (2H, s, CH_2), 2.43 (3H, s, CH_3), 1.70 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 192.3, 164.8, 160.2, 144.5, 132.8, 129.0, 127.8, 106.6, 96.3, 42.6, 24.4, 21.1; *m/z* (EI-MS) 283.1 $(M+Na)^+$.

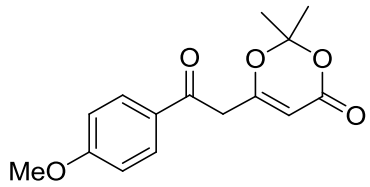
2,2-Dimethyl-6-(2-oxo-2-*p*-fluoro-phenylethyl)-4H-1,3-dioxin-4-one 105. This compound is novel.



This compound was prepared following the general procedure above using diisopropylamine (0.3 g, 3.0 mmol), *n*-BuLi (2.0 cm^3, 3.2 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (0.32 g, 2.2 mmol) and1-*p*-fluorobenzoylbenzotriazole (0.48 g, 2.0 mmol) and the product was isolated as described above as light yellow crystals (0.20 g, 0.76

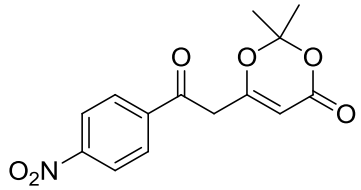
mmol, 38%). MP 118 °C; (found (ESI): M^+ + Na, 287.0690. $C_{14}H_{13}FO_4$ requires M, 287.0695); ν_{max} 1731, 1688, 1595, 1377, 1202, 1016, 986, 837, 813 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.99-7.96 (2H, m, Ar), 7.20-7.16 (2H, m, Ar), 5.42 (1H, s, =CH), 3.88 (2H, s, CH_2), 1.71 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 191.5, 167.5, 164.9, 160.7, 132.3, 131.1 (d, *J* 9.5), 116.1 (d, *J* 22.0), 107.4, 97.1, 43.2, 25.0; *m/z* (EI-MS) 287.1 $(M+Na)^+$.

2,2-Dimethyl-6-(2-oxo-2-*p*-methoxyl-phenylethyl)-4H-1,3-dioxin-4-one 106. This compound is novel.



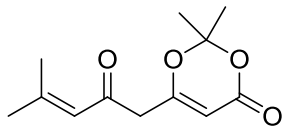
This compound was prepared following the general procedure above using diisopropylamine (1.5 g, 15.0 mmol), *n*-BuLi (10.3 cm^3, 16.5 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (1.70 g, 11.4 mmol) and1-*p*-methoxylbenzoylbenzotriazole (2.53 g, 10.0 mmol) and the product was isolated as described above as a light yellow solid (1.1 g, 3.9 mmol, 39%). (found (ESI): M^+ + Na, 299.0890. $C_{15}H_{16}O_5$ requires M, 299.0895); ν_{max} 1722, 1678, 1595, 1375, 1258, 1220, 1203, 1189, 1164, 1016, 1003, 988, 834, 811 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.91 (2H, d, *J* 8.9, Ar), 6.96 (2H, d, *J* 8.9, Ar), 5.41 (1H, s, =CH), 3.89 (3H, s, OCH_3), 3.85 (2H, s, CH_2), 1.70 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 191.5, 165.4, 164.2, 160.9, 130.7, 128.9, 114.1, 107.3, 96.8, 55.6, 43.1, 25.0; *m/z* (EI-MS) 299.1 $(M+Na)^+$.

2,2-Dimethyl-6-(2-oxo-2-*p*-nitro-phenylethyl)-4H-1,3-dioxin-4-one 107. This compound is novel.



This compound was prepared following the general procedure above using diisopropylamine (0.15 g, 1.5 mmol), *n*-BuLi (1.0 cm^3, 1.6 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (0.16 g, 1.1 mmol) and1-*p*-nitrobenzoylbenzotriazole (0.27 g, 1.0 mmol) and the product was isolated as described above as a light yellow solid (0.1 g, 0.36 mmol, 36%). MP 74 °C; (found (ESI): M^+ + Na, 314.0635. $C_{14}H_{13}NO_6$ requires M, 314.0640); ν_{max} 1720, 1693, 1529, 1376, 1345, 1319, 1199, 1015, 989, 849, 815, 746 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.36 (2H, d, *J* 8.8, Ar), 8.12 (2H, d, *J* 8.8, Ar), 5.46 (1H, s, =CH), 3.97 (2H, s, CH_2), 1.72 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 191.7, 164.0, 160.5, 150.8, 140.1, 129.4, 124.1, 107.5, 97.4, 43.6, 25.0; *m/z* (EI-MS) 314.1 $(M+Na)^+$.

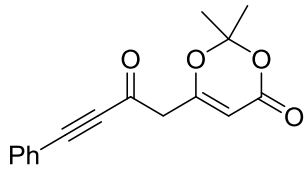
2,2-Dimethyl-6-(2-oxo-4-phenylpropynyl)-4H-1,3-dioxin-4-one 108. This compound is novel.



This compound was prepared following the general procedure above using diisopropylamine (0.77 g, 7.5 mmol), *n*-BuLi (5.2 cm^3, 8.3 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (0.85 g, 5.7 mmol) and 1-(3-methyl-1-oxo-2-butenyl)-benzotriazole (1.0 g, 5.0 mmol) and the product was isolated as described above as light yellow oil (0.31 g, 1.4 mmol, 28%); (found (ESI): $2M^+$ + Na, 471.1989. $C_{24}H_{32}O_8$ requires M, 471.1994); ν_{max}1724, 1691, 1617, 1372, 1270, 1201, 1013, 991 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.09 (1H, s, $(CH_3)_2C=CH$), 5.35 (1H, s, =CH), 3.33 (2H, s, CH_2), 2.17 (3H, s, $CH_3C=$), 1.94 (3H, s,

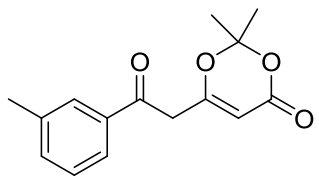
CH_3C=), 1.71 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 192.2, 165.4, 160.8, 159.2, 122.4, 107.0, 96.3, 48.5, 27.8, 25.0, 21.1; *m/z* (EI-MS) 470.9 $(2M+Na)^+$.

2,2-Dimethyl-6-(2-oxo-4phenylacryloyl)-4H-1,3-dioxin-4-one 109. This compound is novel.



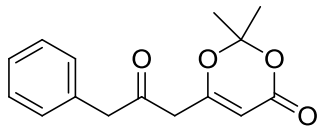
This compound was prepared following the general procedure above using diisopropylamine (0.71 g, 7.5 mmol), *n*-BuLi (5.2 cm^3, 8.25 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (0.85 g, 5.7 mmol) and 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (1.14 g, 5.0 mmol) and the product was isolated as described above as a brown solid (0.19 g, 0.70 mmol, 15%). MP 60 °C; (found (ESI): M^+ + Na, 293.0784. $C_{16}H_{14}O_4$ requires M, 293.0789); ν_{max} 2198,1725, 1671, 1373, 1273, 1074, 1014, 769, 690cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.57 (1H, d, *J* 8.5, Ph), 7.50 (1H, t, *J* 8.7, Ph), 7.43-7.39 (2H, m, Ph), 5.48 (1H, s, =CH), 3.58 (2H, s, CH_2), 1.73 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 179.4, 163.3, 160.6, 133.3, 131.5, 128.9, 119.1, 107.4, 97.3, 93.6, 87.1, 49.5, 25.0; *m/z* (EI-MS) 293.1 $(M+Na)^+$.

2,2-Dimethyl-6-(2-oxo-2-*m*-methyl-phenylethyl)-4H-1,3-dioxin-4-one 110. This compound is novel.



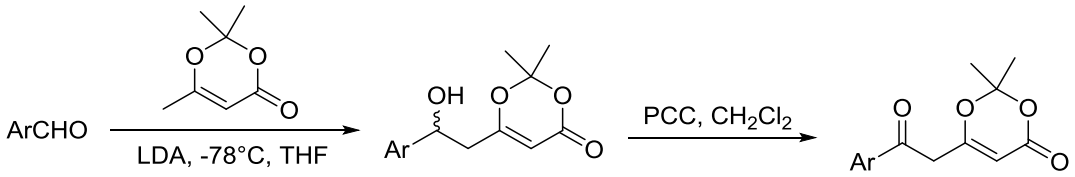
This compound was prepared following the general procedure above using diisopropylamine (1.50 g, 15 mmol), *n*-BuLi (10.2 cm^3, 16.6 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (1.70 g, 11.2 mmol) and 1-*m*-toluoylbenzotriazole (2.4 g, 10 mmol) and the product was isolated as described above as a light yellow solid (1.20 g, 4.6 mmol, 46%). MP 81 °C; (found (ESI): M^+ + Na, 283.0941. $C_{15}H_{16}O_4$ requires M, 283.0946); ν_{max} 1727, 1682, 1644, 1389, 1372, 1271, 1160, 1242, 1182, 1015, 802 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.75 (1H, s, Ar), 7.73 (1H, d, *J* 8.6, Ar), 7.45-7.36 (2H, m, Ar), 5.41 (1H, s, =CH), 3.89 (2H, s, CH_2), 2.43 (3H, s, CH_3), 1.70 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 193.3, 165.3, 160.8, 138.8, 135.9, 134.8, 128.81, 128.78, 125.6, 107.3, 96.9, 43.3, 25.0, 21.3; *m/z* (EI-MS) 283.1 $(M+Na)^+$.

2,2-Dimethyl-6-(2-oxo-3-phenylpropyl)-4H-1,3-dioxin-4-one 111. This compound is novel.



This compound was prepared following the general procedure above using diisopropylamine (1.50 g, 15 mmol), *n*-BuLi (10.2 cm^3, 16.6 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one(1.70 g, 11.2 mmol) and 1-*m*-toluoylbenzotriazole (2.4 g, 10 mmol) and the product was isolated as described above as a white solid (78 mg, mmol, 15%). MP 81 °C; (found (ESI): M^+ + Na, 283.0941. $C_{15}H_{16}O_4$ requires M, 283.0946); ν_{max} 1727, 1682, 1644, 1389, 1372, 1271, 1160, 1242, 1182, 1015, 802 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.75 (1H, s, Ar), 7.73 (1H, d, *J* 8.6, Ar), 7.45-7.36 (2H, m, Ar), 5.41 (1H, s, =CH), 3.89 (2H, s, CH_2), 2.43 (3H, s, CH_3), 1.70 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 200.3, 163.9, 160.3, 132.2, 128.9, 128.4, 127.0, 106.7, 96.1, 49.7, 45.5, 24.4; *m/z* (EI-MS) 283.1 $(M+Na)^+$.

General Procedure [3]



To a solution of diisopropylamine (3.1 g, 30 mmol) in THF (40 cm^3) at –78 °C was added *n*-BuLi (1.6 M in hexane, 20.6 cm^3, 33 mmol) dropwise over 20 min then a solution of 2,2,6-trimethyl-1,3-dioxin-4-one (3.70 g, 26.0 mmol) in THF (20 cm^3) was added dropwise over 20 min. After stirring for 1.5 h, a solution of aromatic aldehyde (22 mmol, aldehydes were used directly without distillation) in THF (10 cm^3) was added in one portion. The resulting mixture was stirred at –78 °C for 1 h and sat NH_4Cl (40 cm^3) was added to quench the reaction. The mixture was extracted with ethyl acetate (3 × 20 cm^3) and the combined organic phase was washed with brine (10 cm^3), dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=5:1-3:1).

To a solution of alcohol (27.4 mmol) in CH_2Cl_2 (130 cm^3) PCC powder (14.8 g, 68.5 mmol) was added. The mixture was stirred at rt for 6 h. After reaction complete solid was filtered and washed with CH_2Cl_2 (3 × 30 cm^3). The combined organic phase was concentrated and the crude product was purified directly by silica gel column chromatography (eluent hexane/EtOAc/DCM=4:1:0.5).

Only full data for new compounds were given. Full data for alcohols will be found in the next section.

6-(2-Hydroxy-2-thienylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 129.

This compound was prepared following the general procedure above using diisopropylamine (2.06 g, 20.0 mmol), *n*-BuLi (13.7 cm^3, 23.0 mmol), 2,2,6-trimethyl-1,3-

dioxin-4-one(2.35 g, 16.5 mmol), 2-thiophenecarbaldehyde (1.61 g, 14.4 mmol) and the product was isolated as described above as brown oil (2.20 g, 8.4 mmol, 58%).

6-(2-Hydroxy-2-p-bromo-phenylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 118.

This compound was prepared following the general procedure above using diisopropylamine (3.10 g, 30.0 mmol), n-BuLi (20.6 cm3, 33.0 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (3.70 g, 26.0 mmol), 4-bromobenzaldehyde (4.07 g, 22.0 mmol) and the product was isolated as white crystals (4.22 g, 12.9 mmol, 60%).

6-(2-Hydroxy-2-*p*-nitro-phenylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 115.

This compound was prepared following the general procedure above using diisopropylamine (3.10 g, 30.0 mmol), *n*-BuLi (20.6 cm^3, 33.0 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (3.70 g, 26.0 mmol), 4-nitrobenzaldehyde (3.32 g, 22.0 mmol) and the product was isolated as light yellow crystals (4.27 g, 14.4 mmol, 66%).

6-(2-Hydroxy-2-*p*-methyl-phenylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 116.

This compound was prepared following the general procedure above using diisopropylamine (3.10 g, 30.0 mmol), *n*-BuLi (20.6 cm^3, 33.0 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (3.70 g, 26.0 mmol), 4-methylbenzaldehyde (2.64 g, 22.0 mmol) and the product was isolated as described above as white crystals (3.48 g, 13.3 mmol, 60%).

6-(2-Hydroxy-2-*m*-methyl-phenylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 117.

This compound was prepared following the general procedure above using diisopropylamine (3.10 g, 30.0 mmol), *n*-BuLi (20.6 cm^3, 33.0 mmol), 2,2,6-trimethyl-1,3-

dioxin-4-one (3.70 g, 26.0 mmol), 3-methylbenzaldehyde (2.64 g, 22.0 mmol) and the product was isolated as colourless oil (4.69 g, 17.9 mmol, 81%).

6-(2-Hydroxy-2-o-methyl-phenylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 120.

This compound was prepared following the general procedure above using diisopropylamine (1.55 g, 15.0 mmol), *n*-BuLi (10.3 cm3, 16.5 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (1.85 g, 13.0 mmol), 2-methylbenzaldehyde (1.32 g, 11.0 mmol) and the product was isolated as white crystals (2.43 g, 9.3 mmol, 84%).

6-(2-Hydroxy-2-p-fluoro-phenylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 121.

This compound was prepared following the general procedure above using diisopropylamine (3.10 g, 30.0 mmol), *n*-BuLi (20.6 cm3, 33.0 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (3.70 g, 26.0 mmol), 4- fluorobenzaldehyde (2.73 g, 22.0 mmol) and the product was isolated as white crystals (4.76 g, 17.9 mmol, 81%).

6-(2-Hydroxy-2-*p*-methoxyl-phenylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 122.

This compound was prepared following the general procedure above using diisopropylamine (3.10 g, 30.0 mmol), *n*-BuLi (20.6 cm^3, 33.0 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (3.70 g, 26.0 mmol), 4-methoxybenzaldehyde (2.72 g, 20.0 mmol) and the product was isolated as white crystals (4.28 g, 15.4 mmol, 77%).

2,2-Dimethyl-6-(2-oxo-2-phenylethyl)-4H-1,3-dioxin-4-one 99.

This compound was prepared following the general procedure above using alcohol **114** (6.80 g, 27.4 mmol) and PCC (14.0 g, 68.5 mmol). The product was isolated as light yellow solid (6.03 g, 24.5 mmol, 89%).

2,2-Dimethyl-6-(2-oxo-2-p-nitro-phenylethyl)-4H-1,3-dioxin-4-one 107.

This compound was prepared following the general procedure above using alcohol **115** (1.63 g, 5.6 mmol) and PCC (3.0 g, 14.0 mmol). The product was isolated as light yellow solid (765 mg, 2.6 mmol, 46%).

2,2-Dimethyl-6-(2-oxo-2-*p*-methyl-phenylethyl)-4H-1,3-dioxin-4-one 104.

This compound was prepared following the general procedure above using alcohol **116** (936 mg, 3.6 mmol) and PCC (1.95 g, 9.0 mmol). The product was isolated as white solid (679 mg, 2.6 mmol, 73%).

2,2-Dimethyl-6-(2-oxo-2-m-methyl-phenylethyl)-4H-1,3-dioxin-4-one 110.

This compound was prepared following the general procedure above using alcohol **117** (1.78 g, 6.8 mmol) and PCC (3.68 g, 17.0 mmol). The product was isolated as white solid (1.45 g, 5.6 mmol, 81%).

2,2-Dimethyl-6-(2-oxo-2-o-methyl-phenylethyl)-4H-1,3-dioxin-4-one 102.

This compound was prepared following the general procedure above using alcohol **120** (1.89 g, 7.2 mmol) and PCC (3.9 g, 18.1 mmol) and the product was isolated as light yellow solid (1.26 g, 4.8 mmol, 67%).

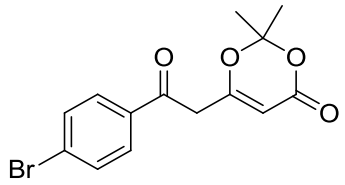
2,2-Dimethyl-6-(2-oxo-2-p-fluoro-phenylethyl)- 4H-1,3-dioxin-4-one 105.

This compound was prepared following the general procedure above using alcohol **121** (1.23 g, 4.6 mmol) and PCC (2.5 g, 11.6 mmol) and the product was isolated as white crystals (791mg, 3.0 mmol, 64%).

2,2-Dimethyl-6-(2-oxo-2-p-methoxyl-phenylethyl)-4H-1,3-dioxin-4-one 106.

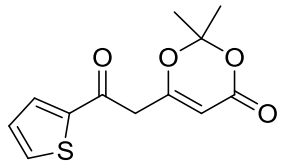
This compound was prepared following the general procedure above using alcohol **122** (1.41 g, 5.1 mmol), PCC (2.78 g, 12.8 mmol). The product was isolated as described above as white crystals (1.31 g, 4.7 mmol, 93%).

2,2-Dimethyl-6-(2-oxo-2-*p*-bromo-phenylethyl)-4H-1,3-dioxin-4-one 112. This compound is novel.



This compound was prepared following the general procedure above using alcohol (1.93 g, 5.9 mmol) and PCC (3.2 g, 14.8 mmol) and the product was isolated as white crystals (1.50 g, 4.6 mmol, 80%). MP 98 °C; (found (ESI): M^+ + Na, 346.9889. $C_{14}H_{13}{}^{79}BrO_4$ requires M, 346.9894); ν_{max} 1723, 1688, 1636, 1583, 1387, 1376, 1200, 832, 805 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.6, Ar), 7.65 (2H, d, *J* 8.6, Ar), 5.42 (1H, s, =CH), 3.87 (2H, s, CH_2), 1.71 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 193.7, 164.7, 160.6, 134.6, 132.3, 129.8, 129.4, 107.4, 97.1, 43.2, 25.0; *m/z* (EI-MS) 348.9 $(M+Na)^+$.

2,2-Dimethyl-6-(2-oxo-thienylethyl)-4H-1,3-dioxin-4-one 113. This compound is known and has been fully characterized.[171a]



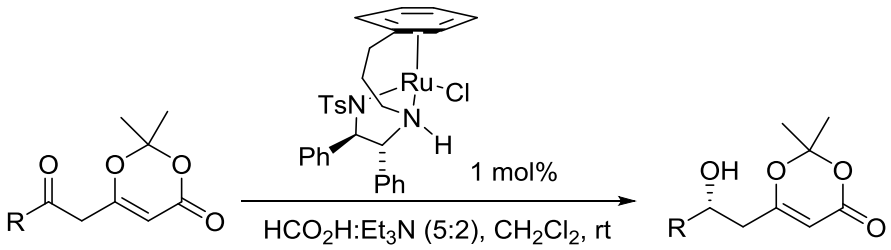
This compound was prepared following the general procedure above using alcohol (1.02 g, 4.0 mmol), PCC (2.17 g, 10.0 mmol). The product was as light yellow solid (778 mg, 3.1 mmol, 76%). ν_{max} 1724, 1656, 1637, 1414, 1354, 1374, 1227, 1201, 1014, 819, 733 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.78 (1H, d, *J* 3.8, Ar), 7.75 (1H, d, *J* 5.0, Ar), 7.18 (1H, dd, *J* 5.0, 3.8, Ar), 5.45 (1H, s, =CH), 3.87 (2H, s, CH_2), 1.70 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 185.7, 164.7, 160.7, 142.9, 135.2, 133.3, 133.2, 128.5, 107.3, 96.9, 43.8, 24.9; *m/z* (EI-MS) 275.0 $(M+Na)^+$.

6-(2-Hydroxy-2-phenylethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 114.

This compound was prepared following the general procedure above using diisopropylamine (3.10 g, 30.0 mmol), *n*-BuLi (20.6 cm^3, 33.0 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (3.70 g, 26.0 mmol), benzaldehyde (2.33 g, 22.0 mmol) and the product was isolated as white crystals (3.58 g, 14.4 mmol, 66%).

3.6. Asymmetric Transfer Hydrogenation of 2,2-Dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones.

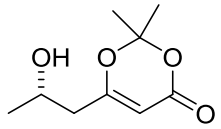
General Procedure



(*R*,*R*)-**c2** (0.5 mg, 8 × 10^{-4} mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture (32.5 mg) and 2,2-dimethyl-6-(2-oxoalkylethyl)-1,3-dioxin-4-one (8 × 10^{-2} mmol) in degassed CH_2Cl_2 (0.5 cm^3) was injected under a nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed. After the reaction was

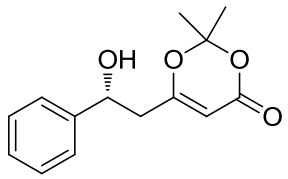
complete, the reaction mixture was directly purified by silica gel column chromatography (eluent hexane/EtOAc=3:1) to give the product.

6-[(2*R*)-2-Hydroxypropyl]-2,2-dimethyl-4H-1,3-dioxin-4-one *S*-128. This compound is known but not fully characterized.[172]



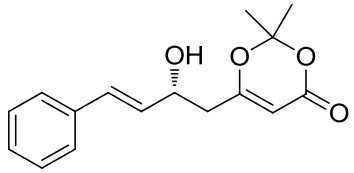
This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.5 mg, 8×10^{-4} mmol), ketone (14.7 mg, 8.0×10^{-2} mmol), HCO_2H/Et_3N 5:2 (32.5 mg), and the product was isolated as described above as a colourless oil (13.5 mg, 0.072 mmol, 91%, 59% ee). $[\alpha]_D^{24}$ +19.7 (c 1.33 in $CHCl_3$) 59% ee (*S*); $[\alpha]_D$+25.2 (c 1.0 in $CHCl_3$) 90% ee (*S*);[172] (found (ESI): M^+ + Na, 209.0788. $C_9H_{14}O_4$ requires M, 209.0789); ν_{max} 3418, 1706, 1630, 1389, 1374, 1272, 1200, 802 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.33 (1H, s, =CH), 4.16-4.08 (1H, m, C*H*OH), 2.38 (1H, d, *J* 2.8, HC*H*), 2.37 (1H, s, HC*H*), 1.70 (6H, s, $2CH_3$), 1.27 (3H, d, *J* 6.2, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 169.3, 161.3, 106.6, 94.9, 65.1, 43.2, 25.2, 24.9, 23.5; *m/z* (EI-MS) 209.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 98:2, 1.0 cm^3/min, T = 20 °C. Retention times: (major - *R*) 70.3 min, (minor - *S*) 77.6 min.

6-[(2*R*)-2-Hydroxy-2-phenylethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one *R*-114. This compound is known and has been fully characterized.[88a]



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.5 mg, 8×10^{-4} mmol), ketone (19.8 mg, 8.0×10^{-2} mmol), HCO_2H/Et_3N 5:2 (32.5 mg), and the product was isolated as described above as white crystals (17.6 mg, 0.072 mmol, 89%, 98% ee). $[\alpha]_D^{26}$ +44.9 (c 0.7 in $CHCl_3$) 98% ee (*R*); lit. $[\alpha]_D^{19}$ +35.9 (c 1.0 in $CHCl_3$) 84% ee (*R*);[88a] (found (ESI): M^+ + Na, 271.0941. $C_{14}H_{16}O_4$ requires M, 271.0946); ν_{max} 3430, 1691, 1635, 1375, 1277, 1203, 1020, 810 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41-7.27 (5H, m, Ph), 5.30 (1H, s, =CH), 4.98 (1H, dd, *J* 8.6, 4.9, C*H*OH), 2.69 (1H, dd, *J* 14.6, 8.6, HC*H*), 2.60 (1H, dd, *J* 14.6, 4.9, HC*H*), 2.43 (1H, br, OH), 1.67 (3H, s, CH_3), 1.65 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 167.8, 160.5, 142.1, 128.1, 127.7, 125.1, 106.1, 94.7, 70.6, 42.6, 24.8, 24.1; *m/z* (EI-MS) 271.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T = 20 °C. Retention times: (major - *R*) 19.3 min, (minor - *S*) 26.6 min.

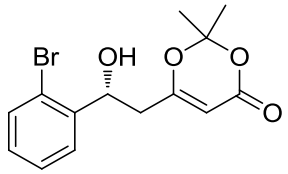
6-[(2*R*,3*E*)-2-Hydroxy-4-phenyl-3-buten-1-yl]-2,2-dimethyl-4H-1,3-dioxin-4-one ***R*-120.** This compound is known and has been fully characterized.[88b]



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.5 mg, 8×10^{-4} mmol), ketone (22.0 mg, 8×10^{-2} mmol), HCO_2H/Et_3N 5:2 (32.5 mg), and the product was isolated as described above as white crystals (22.0 mg, 0.080 mmol, 99%, 79% ee). $[\alpha]_D^{24}$ +7.2 (c 0.63 in $CHCl_3$) 79% ee (*R*); lit. $[\alpha]_D^{19}$ +6.2 (c 1.0 in $CHCl_3$) 92% ee (*R*);[88b] (found (ESI): M^+ + Na, 297.1097. $C_{16}H_{18}O_4$ requires M, 297.1102); ν_{max} 3382, 1713, 1626, 1396, 1377, 1279, 1200, 1015, 967, 792, 744, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27-7.15 (5H, m, Ph), 6.53 (1H, d, *J* 15.9, =CHPh), 6.10 (1H, dd, *J* 15.9, 6.6,

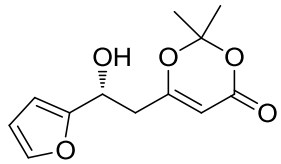
=C*H*CHOH), 5.25 (1H, s, C=CH), 4.51-4.45 (1H, m, C*H*OH), 2.44-2.42 (2H, m, CH_2), 2.23 (1H, br, OH), 1.58 (3H, s, CH_3), 1.57 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 167.8, 160.6, 135.4, 130.8, 129.7, 128.1, 127.5, 125.9, 106.1, 94.8, 69.1, 40.9, 24.7, 24.3; *m/z* (EI-MS) 297.1 $(M+Na)^+$; HPLC separation conditions: CHIRALCEL OD column (250 mm × 4.6 mm), hexane:*i*-PrOH 80:20, 0.8 cm^3/min, T = 17 °C. Retention times: (major - *R*) 19.5 min, (minor - *S*) 46. 0 min.

6-[(2*R*)-2-Hydroxy-2-*o*-bromo-phenylethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one *R*-126. This compound is novel.



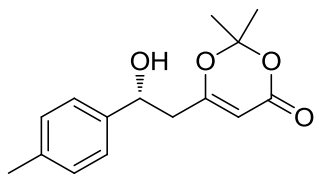
This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.5 mg, 8×10^{-4} mmol), ketone (26.0 mg, 8.0×10^{-2} mmol), HCO_2H/Et_3N 5:2 (32.5 mg), and the product was isolated as described above as white solid (22.0 mg, 0.070 mmol, 88%, 82% ee). $[\alpha]_D^{20}$ +132.1 (c 0.25 in $CHCl_3$) 82% ee (*R*); (found (ESI): M^+ + Na, 349.0046. $C_{14}H_{15}{}^{79}BrO_4$ requires M, 349.0051); ν_{max} 3414, 1707, 1630, 1389, 1374, 1273, 1200, 1016, 803, 755 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.67 (1H, dd, *J* 7.7, 1.6, Ar), 7.50 (1H, dd, *J* 8.0, 1.2, Ar), 7.34 (1H, td, *J* 7.5, 1.0, Ar), 7.14 (1H, td, *J* 7.5, 1.6, Ar), 5.35 (1H, s, C=CH), 5.32 (1H, dd, *J* 9.3, 3.4, C*H*OH), 2.73 (1H, dd, *J* 14.8, 3.4, HC*H*), 2.48 (1H, dd, *J* 14.8, 9.3, HC*H*), 2.19 (1H, br, OH), 1.69 (3H, s, CH_3), 1.66 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 167.9, 164.2, 141.1, 132.2, 128.9, 127.4, 126.6, 120.9, 106.2, 94.6, 69.5, 40.9, 24.7, 24.1; *m/z* (EI-MS) 349.0 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T= 20 °C. Retention times, (major - *R*) 10.9 min, (minor - *S*) 12.7 min.

6-[(2*R*)-2-(2-Furanyl)-2-hydroxyethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one ***R*****-123.** This compound is known and has been fully characterized.[88a]



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.5 mg, 8×10^{-4} mmol), ketone (18.9 mg, 8.0×10^{-2} mmol), HCO_2H/Et_3N 5:2 (32.5 mg), and the product was isolated as described above as a white solid (17.3 mg, 0.073 mmol, 91%, 99% ee). $[\alpha]_D^{24}$ +28.0 (c 0.70 in $CHCl_3$) 99 % ee (*R*); lit. $[\alpha]_D^{25}$ +27.0 (c 0.58 in $CHCl_3$) 94% ee (*R*);[88a] (found (ESI): M^+ + Na, 261.0733. $C_{12}H_{14}O_5$ requires M, 261.0739); ν_{max} 3404, 1703, 1623, 1390, 1374, 1274, 1201, 1009, 807, 740 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39 (1H, d, *J* 2.0, Ar), 6.34 (1H, dd, *J* 3.2, 2.0, Ar), 6.28 (1H, d, *J* 3.2, Ar), 5.32 (1H, s, C=CH), 5.00 (1H, t, *J* 7.0, C*H*OH), 2.80-2.78 (2H, m, CH_2), 2.56 (1H, br, OH), 1.67 (1H, s, CH_3), 1.64 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 167.8, 161.2, 154.7, 142.5, 110.4, 106.8, 106.6, 95.5, 64.5, 39.8, 25.2, 24.8; *m/z* (EI-MS) 261.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T= 20 °C. Retention times, (major - *R*) 12.7 min, (minor - *S*) 14.1 min.

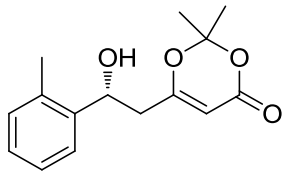
6-[(2*R*)-2-Hydroxy-2-*o*-methyl-phenylethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one ***R*****-116.** This compound is known but not fully characterized.[173]



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.5 mg, 8×10^{-4} mmol), ketone (20.1 mg, 8.0×10^{-2} mmol), HCO_2H/Et_3N 5:2 (32.5 mg), and

the product was isolated as described above as white crystals (19.3 mg, 0.077 mmol, 96%, 97% ee). $[\alpha]_D^{20}$ +40.6 (c 1.6 in $CHCl_3$) 97 % ee (*R*); (found (ESI): M^+ + Na, 285.1097. $C_{15}H_{18}O_4$ requires M, 285.1102); ν_{max} 3371, 1708, 1629, 1394, 1376, 1275, 1183, 1066, 1028, 1012, 795, 773 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.0, Ar), 7.15 (2H, d, *J* 8.0, Ar), 5.25 (1H, s, =CH), 4.91 (1H, dd, *J* 8.6, 4.8, C*H*OH), 2.66 (1H, dd, *J* 14.6, 8.6, *H*CH), 2.56 (1H, dd, *J* 14,6, 4.8, *H*CH), 2.34 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.63 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.7, 161.4, 139.9, 137.9, 129.3, 125.7, 106.7, 95.2, 70.9, 43.1, 25.4, 24.7, 21.1; *m/z* (EI-MS) 285.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm) hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T = 19 °C. Retention times, (major - *R*) 14.1 min, (minor - *S*) 25.8 min.

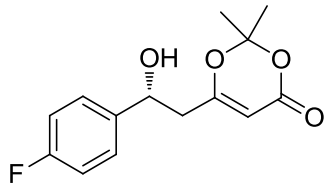
6-[(2*R*)-2-Hydroxy-2-*o*-methyl-phenylethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one ***R*-120.** This compound is known but not fully characterized.[173]



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.5 mg, 8×10^{-4} mmol), ketone (20.1 mg, 8.0×10^{-2} mmol), HCO_2H/Et_3N 5:2 (32.5 mg), and the product was isolated as described above as white crystals (18.1 mg, 0.072 mmol, 90%, 98% ee). $[\alpha]_D^{24}$ +55.9 (c 3.0 in $CHCl_3$) 98% ee (*R*); (found (ESI): M^+ + H, 263.1281. $C_{15}H_{18}O_4$ requires M, 263.1283); ν_{max} 3429, 1704, 1631, 1389, 1374, 1273, 1254, 1201, 1015, 804, 758 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.47 (1H, d, *J* 7.4, Ar), 7.27-7.12 (3H, m, Ar), 5.32 (1H, s, =CH), 5.19 (1H, dd, *J* 8.5, 4.5, C*H*OH), 2.63-2.52 (2H, m, CH_2), 2.34 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.64 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.9, 160.4, 141.0, 134.2, 130.6, 127.8, 126.5, 125.1, 106.7, 95.1, 67.5, 42.1, 25.4, 24.6, 18.9; *m/z* (EI-MS)

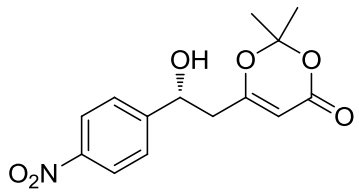
263.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T = 19 °C. Retention times, (major - *R*) 12.8 min, (minor - *S*) 12.9 min.

6-[(2R)-2-Hydroxy-2-*p*-fluoro-phenylethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one *R*-**121.** This compound is novel.



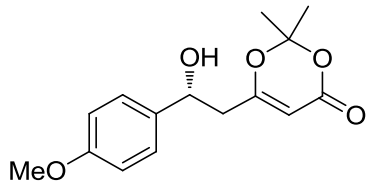
This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.5 mg, 8×10^{-4} mmol), ketone (21.1 mg, 8.0×10^{-2} mmol), HCO_2H/Et_3N 5:2 (32.5 mg), and the product was isolated as described above as white crystals (20.8 mg, 0.078 mmol, 98%, 99% ee). MP 89 °C; $[\alpha]_D^{24}$ +45.3 (c 0.62 in $CHCl_3$) 99% ee (*R*); (found (ESI): M^+ + Na, 289.0847. $C_{14}H_{15}FO_4$ requires M, 289.0852); ν_{max} 3357, 1705, 1509, 1396, 1377, 1260, 1063, 1014 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36-7.32 (2H, m, Ar), 7.06-7.02 (2H, m, Ar), 5.28 (1H, s, =CH), 4.95 (1H, dd, *J* 8.6, 4.8, C*H*OH), 2.87 (1H, br, OH), 2.66 (1H, dd, *J* 14.6, 8.6, HC*H*), 2.56 (1H, dd, *J* 14.6, 4.8, HC*H*), 1.67 (3H, s, CH_3), 1.65 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.5, 163,7, 161.3 (d, *J* 15.3), 138.8, 127.4 (d, *J* 8.2), 115.5 (d, *J* 21.5), 106.8, 95.3, 70.4, 43.3, 25.3, 24.7; *m/z* (EI-MS) 289.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane: *i*-PrOH 90:10, 0.6 cm^3/min, T = 19 °C. Retention times, (major - *R*) 21.9 min, (minor - *S*) 25.4 min.

6-[(2*R*)-2-Hydroxy-2-*p*-nitro-phenylethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one *R*-**115.** This compound is known and has been fully characterized.[174]



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.5 mg, 8×10^{-4} mmol), ketone (23.3 mg, 8.0×10^{-2} mmol), HCO_2H/Et_3N 5:2 (32.5 mg), and the product was isolated as described above as white crystals (21.9 mg, 0.075 mmol, 94%, 96% ee). $[\alpha]_D^{24}$ +49.6 (c 0.45 in $CHCl_3$) 96% ee (*R*); $[\alpha]_D^{25}$ +21 (c 1.2 in $CHCl_3$) 75% ee (*R*);[174] (found (ESI): M^+ + Na, 317.0796. $C_{14}H_{15}NO_6$ requires M, 317.0797); ν_{max} 3314, 1704, 1515, 1400, 1380, 1348, 1281, 1085, 1009, 845, 790 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.22 (2H, d, *J* 8.6, Ar), 7.57 (2H, d, *J* 8.6, Ar), 5.35 (1H, s, =CH), 5.13 (1H, t, *J* 3.0, C*H*OH), 3.09 (1H, br, OH), 2.64 (1H, d, *J* 3.0, HC*H*), 2.63 (1H, s, HC*H*), 1.70 (3H, s, CH_3), 1.69 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 167.8, 161.2, 150.2, 147.6, 126.6, 123.9, 107.0, 95.6, 70.0, 43.3, 25.4, 24.7; *m/z* (EI-MS) 317.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T = 19 °C. Retention times, (major - *R*) 27.1 min, (minor - *S*) 33.9 min.

6-[(2*R*)-2-Hydroxy-2-*o*-methoyl-phenylethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one *R*-**180.** This compound is known and has been fully characterized.[88b]

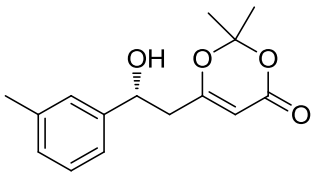


This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (1.8 mg, 3.2×10^{-3} mmol), ketone (90.0 mg, 0.32 mmol), HCO_2H/Et_3N 5:2 (136 mg), and the product was isolated as described above as white crystals (82.4 mg, 0.29 mmol, 92%, 98% ee). $[\alpha]_D^{24}$ +28.8 (c 3.0 in $CHCl_3$) 98% ee (*R*); $[\alpha]_D^{20}$ +33.9 (c 1.2 in $CHCl_3$) 94% ee (*R*);[88b]

(found (ESI): M^+ + Na, 301.1046. $C_{15}H_{18}O_5$ requires M, 301.1051); ν_{max} 3428, 1705, 1631, 1512, 1389, 1374, 1244, 1202, 1175, 1012, 830, 804 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.6, Ar), 6.87 (2H, d, *J* 8.6, Ar), 5.25 (1H, s, =CH), 4.90 (1H, dd, *J* 8.6, 5.0, C*H*OH), 3.79 (3H, s, OCH_3), (1H, dd, *J* 14.6, 8.6, *H*CH), (1H, dd, *J* 14.6, 5.0, *H*CH), 1.64 (3H, s, CH_3), 1.63 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.8, 151.5, 159.4, 135.0, 127.1, 114.0, 106.7, 95.1, 70.6, 55.3, 43.1, 25.3, 24.7; *m/z* (EI-MS) 301.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T = 20 °C. Retention times, (major - *R*) 23.9 min, (minor - *S*) 38.0 min.

6-[(2*R*)-2-Hydroxy-2-*m*-methyl-phenylethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one ***R*-126.**

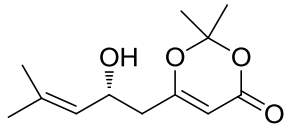
This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (1.2 mg, 2 × 10^{-3} mmol), ketone (52.0 mg, 0.20 mmol), HCO_2H/Et_3N 5:2 (81 mg), and the product was isolated as described above as a colourless oil (49.0 mg, 0.19 mmol, 98%, 98% ee). $[\alpha]_D^{28}$ +36.5 (c 2.0 in $CHCl_3$); (found (ESI): M^+ + Na, 285.1097. $C_{15}H_{18}O_4$ requires M, 285.1102); ν_{max} 3424, 1706, 1613, 1390, 1375, 1272, 1202, 1012, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27-7.22 (1H, m, Ar), 7.17-7.10 (3H, m, Ar), 5.28 (1H, s, =CH), 4.91 (1H, dd, *J* 8.8, 4.7, C*H*OH), 2.81 (1H, br, OH), 2.66 (1H, dd, *J* 14.6, 8.8, *H*CH), 2.57 (1H, dd, *J* 14.6, 4.7, *H*CH), 2.35 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.64 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.7, 161.4, 142.9, 136.4, 128.9, 128.6, 126.4, 122.8, 106.7, 95.2, 71.1, 43.2, 25.4, 24.7, 21.4; *m/z* (EI-MS) 285.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB

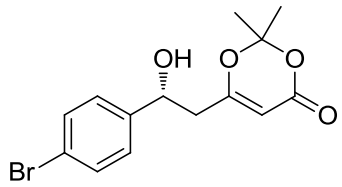
column (250 mm × 4.6 mm) hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T = 28 °C. Retention times, (major - *R*) 12.9 min, (minor - *S*) 19.1 min.

6-[(2*R*)-2-Hydroxy-4,4-dimethylacryloyl]-2,2-dimethyl-4H-1,3-dioxin-4-one ***R*-127.** This compound is known and has been fully characterized.[88b]



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (1.3 mg, 2.3 × 10^{-3} mmol), ketone (51.0 mg, 0.23 mmol), HCO_2H/Et_3N 5:2 (93 mg), and the product was isolated as described above as a colourless oil (9.2 mg, 0.04 mmol, 18%, 70% ee). The yield and ee value of over reduction product were not determined. (found (ESI): M^+ + Na, 249.1097. $C_{12}H_{18}O_4$ requires M, 249.1102); ν_{max} 3426, 1709, 1631, 1389, 1374, 1273, 1202, 1013, 804 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.31 (1H, s, =CH), 5.19 (1H, d, *J* 8.8, $CH_3)_2C=CH$), 4.67-4.62 (1H, m, C*H*OH), 2.59 (1H, dd, *J* 14.4, 7.6, HC*H*), 2.35 (1H, dd, *J*14.4, 5.6, HC*H*), 1.75 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.70 (3H, s, $CH_3C=$), 1.68 (3H, s, $CH_3C=$); δ_C (75 MHz, $CDCl_3$) 168.7, 161.2, 137.0, 126.3, 106.6, 95.1, 66.7, 41.8, 25.7, 25.3, 24.8, 18.3; *m/z* (EI-MS) 475.0 $(2M+Na)^+$; HPLC separation conditions: CHIRALPAK H-OD column (250 mm × 4.6 mm) hexane:*i*-PrOH 95:5, 0.8 cm^3/min, T = 27 °C. Retention times, (major - *R*) 19.1 min, (minor - *S*) 20.3 min.

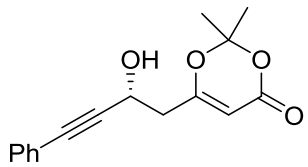
6-[(2*R*)-2-Hydroxy-2-*p*-bromo-phenylethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one ***R*-118.** This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.8 mg, 1.4×10^{-3} mmol), ketone (45.0 mg, 0.138 mmol), HCO_2H/Et_3N 5:2 (60 mg), and the product was isolated as described above as white crystals (39.0 mg, 0.12 mmol, 87%, 98% ee). $[\alpha]_D^{30}$ +39.8 (c 1.5 in $CHCl_3$); MP 80 °C; (found (ESI): M^+ + H, 327.0226. $C_{14}H_{13}O_4{}^{79}Br$ requires M, 327.0232); ν_{max} 3404,1303, 1631, 1390, 1375, 1273, 1201, 1069, 1009, 819, 734 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.50 (2H, d, *J* 8.4, Ar), 7.25 (2H, d, *J* 8.4, Ar), 5.31 (1H, s, =CH), 4.95-4.99 (1H, m, C*H*OH), 2.92 (1H, br, OH), 2.65 (1H, d, *J* 14.7, 8.7, HC*H*), 2.58 (1H, *J* 14.7, 4.6, HC*H*), 1.68 (3H, s, CH_3), 1.67 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.4, 161.4, 142.0, 131.8, 127.5, 121.9, 106.8, 95.3, 70.3, 43.2, 25.4, 24.7; *m/z* (EI-MS) 349.0 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm) hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T = 30 °C. Retention times, (major - *R*) 14.6 min, (minor - *S*) 22.4 min.

6-[(2*R*)-2-Hydroxy-4-phenyl-3-butyn-1-yl]-2,2-dimethyl-4H-1,3-dioxin-4-one ***R*-124.**

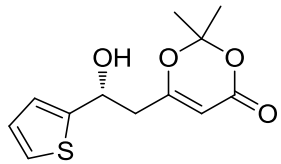
This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.7 mg, 1.1×10^{-3} mmol), ketone (30.4 mg, 0.108 mmol), HCO_2H/Et_3N 5:2 (47 mg), and the product was isolated as described above as a colourless oil (24.8 mg, 0.088 mmol, 82%, 98% ee). $[\alpha]_D^{30}$ +16.2 (c 0.85 in $CHCl_3$); (found (ESI): M^+ + Na, 295.0941 $C_{14}H_{16}O_4$ requires M, 295.0946); ν_{max} 3397, 2234, 1705, 1390, 1375, 1273, 1201, 1013, 756 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41-7.39 (2H, m, Ph), 7.34-7.29 (3H, m, Ph), 5.43 (1H, s, =CH), 4.89-4.86 (1H, m, C*H*OH), 2.78-2.68 (3H, m, CH_2, OH), 1.70 (6H, s, 2 × CH_3); δ_C (75 MHz,

$CDCl_3$) 167.3, 161.2, 131.7, 128.9, 128.5, 121.9, 106.9, 96.0, 88.0, 86.1, 51.7, 42.0, 25.1, 25.0; *m/z* (EI-MS) 295.1 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IA column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:5, 1.0 cm^3/min, T = 30 °C. Retention times: (major - *R*) 36.9 min, (minor - *S*) 39.9 min.

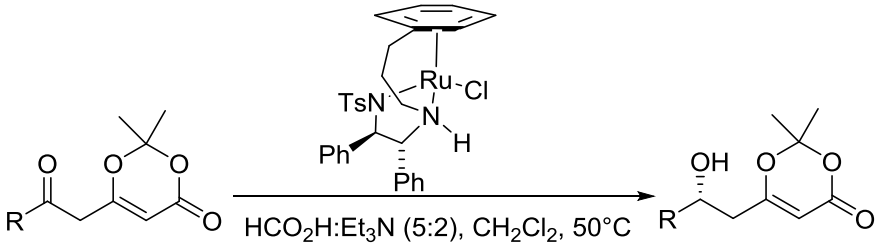
6-[(2*R*)-2-(2-Thienyl)-2-hydroxyethyl]-2,2-dimethyl-4H-1,3-dioxin-4-one ***R*-129.** This compound is known but not fully characterized.[88b]



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (1.7 mg, 2.8×10^{-3} mmol), ketone (70.0 mg, 0.28 mmol), HCO_2H/Et_3N 5:2 (118 mg), and the product was isolated as described above as a white solid (66.2 mg, 0.26 mmol, 95%, 98% ee). $[\alpha]_D^{32}$ +20.7 (c 2.12 in $CHCl_3$) 98% ee (*R*); $[\alpha]_D^{25}$ +24.0 (c 0.88 in $CHCl_3$) 95 % ee (*R*);[88b] (found (ESI): M^+ + Na, 277.0505. $C_{12}H_{14}O_5$ requires M, 277.0510); ν_{max} 3427, 1704, 1632, 1390, 1372, 1273, 1200, 1015, 806, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27-7.26 (1H, d, *J* 2.0, Ar), 7.00-6.95 (2H, m, Ar), 5.29 (1H, s, C=CH), 5.21 (1H, dd, *J* 8.3, 5.1, C*H*OH), 2.91 (1H, br, OH), 2.79 (1H, dd, *J* 14.6, 8.3, HC*H*), 2.71 (1H, dd, *J* 14.6, 5.1, HC*H*), 1.66 (1H, s, CH_3), 1.64 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.1, 161.4, 146.7, 126.8, 125.2, 124.2, 106.8, 96.5, 66.8, 43.3, 25.3, 24.7; *m/z* (EI-MS) 277.0 $(M+Na)^+$; HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T= 30 °C. Retention times, (major - *R*) 15.2 min, (minor - *S*) 18.0 min.

A selection of ketones was reduced by the following reaction conditions at elevated temperature. Experimental results were listed in **Table 9**. The ^1H NMR data of those products were identical to data described above therefore will not be listed here.

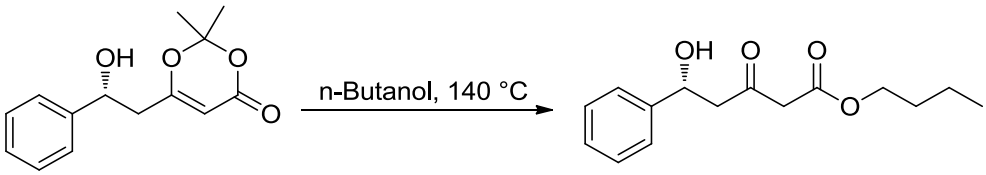
General Procedure



(*R*,*R*)-**c2** (0.6 mg, 1.0×10^{-3} mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture (420 mg) and 2,2-dimethyl-6-(2-oxo-alkylethyl)-1,3-dioxin-4-ones (1.0 mmol) in CH_2Cl_2 (6.0 cm^3) was injected into a flask. The mixture was stirred at 50 °C until starting material was completely consumed (48 h). The mixture was washed with 10% Na_2CO_3 (the amount of Na_2CO_3 solution added was dependant on the amount of formic acid) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=3:1-2/1) to afford the pure product.

3.7. Asymmetric Total Synthesis of Yashabushitriol.

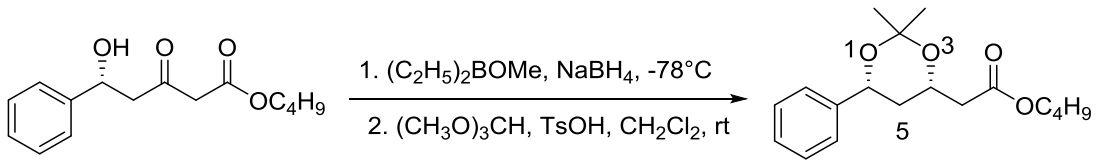
3-Oxo-(5*R*)-hydroxy-benzenepentanoic acid, *n*-butyl ester 132. This compound is novel.



Chiral alcohol *R*-**114** (351 mg, 1.41 mmol) was dissolved in anhydrous *n*-butanol (5 cm^3) and the resulting solution was heated to 140 °C for 1.5 h. After excess *n*-butanol was removed the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=5:1-3:1) to afford product **132** as a colourless oil (330 mg, 1.25 mmol, 88%). $[\alpha]_D^{24}$ + 54.1 (c 0.6 in $CHCl_3$) 98% ee (*R*); (found (ESI): M^+ + Na, 287.1254. $C_{15}H_{20}O_4$ requires M, 287.1259); ν_{max} 3487, 2960, 1735, 1709, 1191, 1058, 699 cm^{-1}; δ_H

(400 MHz, $CDCl_3$) 7.35-7.24 (5H, m, Ph), 5.15 (1H, dt, *J* 9.1, 3.2, C*H*OH), 4.11 (2H, t, *J* 6.7, $COOCH_2$), 3.46 (2H, s, CH_2COO), 3.22 (1H, d, *J* 3.2, OH), 2.97 (1H, dd, *J* 17.3, 9.1, HC*H*CHOH), 2.60 (1H, dd, *J* 17.3, 3.3, HC*H*CHOH), 1.64-1.57 (2H, m, $COOCH_2CH_2$), 1.41-1.32 (2H, m, CH_2CH_3), 0.92 (3H, t, *J* 7.4, CH_3); δ_C (100 MHz, $CDCl_3$) 202.8, 167.0, 142.7, 128.6, 127.8, 125.7, 69.8, 65.4, 51.6, 49.9, 30.5, 19.1, 13.7; *m/z* (ESI-MS) 265.1 $(M+H)^+$.

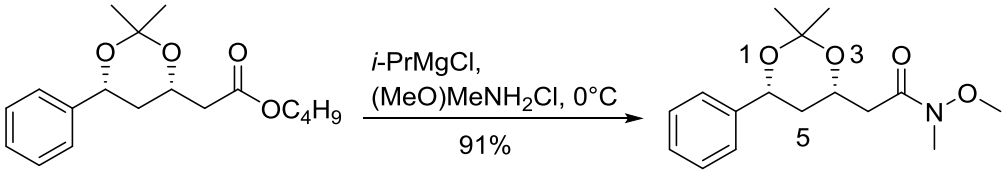
2,2-Dimethyl-(6*R*)-phenyl-1,3-dioxane-(4*S*)-acetic acid, *n*-butyl ester 133. This compound is novel.



Et_2BOMe (1M in THF, 0.65 cm^3, 0.65 mmol) was added dropwise to a solution of β-keto ester **132** (156 mg, 0.59 mmol) in THF (2.8 cm^3) and MeOH (0.7 cm^3) at –78 °C. The mixture was stirred at the same temperature for 20 min then $NaBH_4$ (24.5 mg, 0.65 mmol) was added and the resulting mixture was stirred at -78 °C for 4 h and quenched by sat NH_4Cl (10 cm^3). The aqueous layer was extracted with EtOAc (3 × 30 cm^3) and the combined organic phase was washed with brine (10 cm^3), dried over $MgSO_4$ and concentrated under high vacuum to afford crude diol. 2,2-Dimethoxypropane (620 mg, 6.0 mol) and $TsOH \cdot H_2O$ (5.6 mg, 0.030 mmol) were added to the crude diol and the resulting mixture was stirred at room temperature for 36 h. The reaction was quenched with solid $NaHCO_3$ and washed with Et_2O, concentrated and purified directly by silica gel column chromatography (eluent hexane/EtOAc=15:1) to give the major *syn* product **133** as a colourless oil (124.9 mg, 68% over two steps, diastereomer ratio of *syn*/*anti* was determined to be 5:1 and the two diastereomers can be separated by column

chromatography). $[\alpha]_D^{26}$+ 26.9 (c 0.9 in $CHCl_3$); (found (ESI): M^+ + Na, 329.1723. $C_{18}H_{26}O_4$ requires M, 329.1723); ν_{max} 1732, 1379, 1311, 1198, 1163, 1099, 963, 875, 754, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.31 (4H, m, Ph), 7.29-7.23 (1H, m, Ph), 4.93 (1H, dd, *J* 11.6, 2.6, H-6), 4.47-4.43 (1H, m, H-4), 4.10 (2H, t, *J* 6.6, $COOCH_2$), 2.57 (1H, dd, *J* 15.4, 7.1, CH_2COO), 2.41 (1H, dd, *J* 15.4, 5.9, CH_2COO), 1.83 (1H, dt, *J* 12.9, 2.5, H-5), 1.64-1.56 (5H, m, $COOCH_2CH_2$ and CCH_3), 1.54-1.47 (4H, m, H-5 and CCH_3), 1.43-1.34 (2H, m, CH_2CH_3), 0.93 (3H, t, *J* 7.4, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 171.0, 142.1, 128.5, 127.7, 125.9, 99.3, 71.4, 66.2, 64.4, 41.5, 38.9, 30.7, 30.2, 19.7, 19.1, 13.7; *m/z* (ESI-MS) 329.2 $(M+Na)^+$.

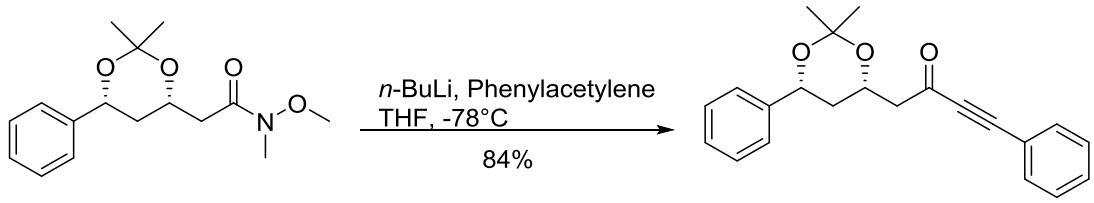
2,2-Dimethyl-(6*R*)-phenyl-1,3-dioxane-(4*S*)-N-methoxy-N-methyl acetamide 134. This compound is novel.



A solution of isopropylmagnesium chloride (2 M in hexane, 0.4 cm^3, 0.8 mmol) was slowly added to a THF (1 cm^3) solution of ester **133** (49 mg, 0.16 mmol) and N,O-dimethylhydroxylamine hydrochloride (38.8 mg, 0.4 mmol) at 0 °C. After stirring for 1 h at 0 °C, the reaction was quenched with sat NH_4Cl solution (2 cm^3) and extracted with EtOAc (3 × 10 cm^3), the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=4:1-2:1) to afford the amide as a white solid (42.5 mg, 0.145 mmol, 91%). MP 70 °C; $[\alpha]_D^{27}$+48.1 (c 0.2 in $CHCl_3$); (found (ESI): M^+ + Na, 316.1519. $C_{16}H_{23}NO_4$ requires M, 316.1519); ν_{max} 2992, 2940, 1657, 1379, 1253, 1198, 1163, 998, 753, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.22 (5H, m, Ph), 4.96 (1H, dd, *J*

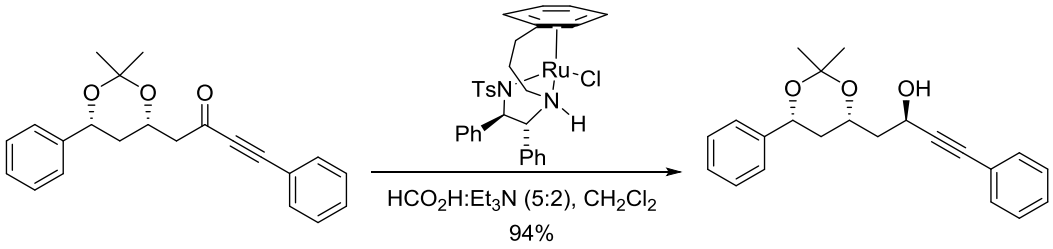
11.6, 2.5, H-6), 4.59-4.53 (1H, m, H-4), 3.69, (3H, s, $NOCH_3$), 3.18 (3H, s, NCH_3), 2.82 (1H, dd, *J* 15.5, 6.0, CH_2CON), 2.49 (1H, dd, *J* 15.5, 6.5, CH_2CON), 1.92 (1H, dt, *J* 12.9, 2.4, H-5), 1.59 (3H, s, CCH_3), 1.49 (3H, m, CCH_3), 1.48 (1H, dd, *J* 12.9, 11.8, H-5); δ_C (100 MHz, $CDCl_3$) 150.8, 142.3, 128.4, 127.5, 125.9, 99.3, 71.4, 66.3, 61.4, 39.3, 38.6, 30.2, 19.9; *m/z* (ESI-MS) 316.1 $(M+Na)^+$.

Compound **135**. This compound is novel.



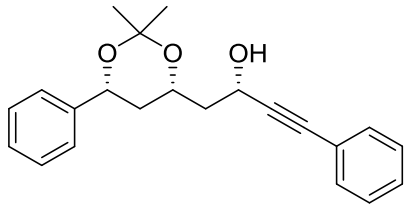
To a solution of phenylacetylene (135 mg, 1.38mmol) in anhydrous THF (6 cm^3) at -78 °C, *n*-BuLi (1.6 M in hexane, 0.73 cm^3, 1.16 mmol) was added in 3 min. The mixture was stirred at -78 °C for 1 h and a Weinreb amide **134** (136.0 mg in 2.0 cm^3 THF, 0.46 mmol) solution was added dropwise. After 30 min at -78 °C, temperature was raised to -10 °C for 2 h and sat NH_4Cl (8 cm^3) was added at -10 °C and the mixture was extracted with EtOAc (3 × 30 cm^3) and combined organic phase was dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=12:1-8:1) to afford the ketone **135** as a colourless oil (129.7 mg, 0.388 mmol, 84%). $[\alpha]_D^{27}$+ 77.8 (c 0.1 in $CHCl_3$); (found (ESI): M^+ + Na, 357.1461. $C_{22}H_{22}O_3$ requires M, 357.1461); ν_{max} 2992, 2202, 1666, 959, 755, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.59-7.25 (10H, m, Ph), 4.98 (1H, d, *J* 11.6, PhC*H*), 4.75-4.67 (1H, m, CH), 2.96 (1H, dd, *J* 16.3, 7.3, HC*H*CO), 2.74 (1H, dd, *J* 16.3, 5.4, *H*CHCO), 1.91-1.84 (1H, m, HC*H*), 1.60 (3H, s, CCH_3), 1.59-1.53 (1H, m, *H*CH), 1.49 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 185.0, 142.1, 133.1, 130.9, 128.7, 128.5, 127.7, 125.9, 119.9, 99.4, 91.3, 88.0, 71.4, 65.6, 51.8, 38.9, 30.1, 19.7; *m/z* (ESI-MS) 357.1 $(M+Na)^+$.

Compound **136**. This compound is novel.



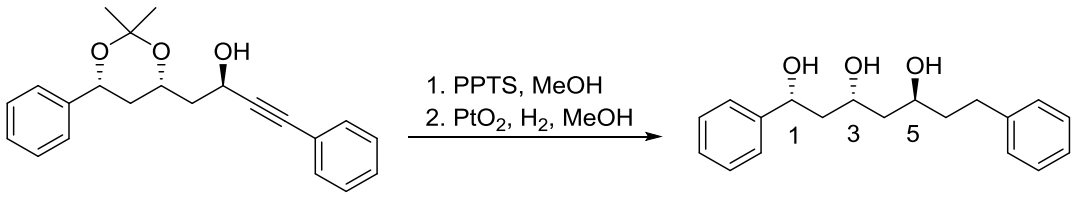
(*R*,*R*)-**c2** (0.3 mg, 5×10^{-4} mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture (28.5 mg) and ketone **135** (22.7 mg, 0.068 mmol) in degassed CH_2Cl_2 (0.5 cm^3) was injected under nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed then the reaction was quenched by sat $NaHCO_3$ (0.5 cm^3) extracted with CH_2Cl_2 (3×6 cm^3) and the combined organic phase was dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=6:1-4:1) to afford the chiral alcohol as colourless oil (21.7 mg, 0.064 mmol, 94%, dr 37/1). $[\alpha]_D^{26}$+ 22.3 (c 0.9 in $CHCl_3$); (found (ESI): M^+ + Na, 359.1618. $C_{22}H_{24}O_3$ requires M, 359.1617); ν_{max} 3426, 2991, 1159, 75, 691 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.45-7.28 (10 H, m, 2 × Ph), 4.99 (1H, dd, *J* 11.5, 2.7, *H*CPh), 4.85-4.81 (1H, m, CHC≡), 4.99 (1H, tt, *J* 10.6, 2.7, CH), 3.57 (1H, d, *J* 8.4, OH), 2.04 (1H, ddd, *J* 14.5, 11.9, 3.1, HC*H*CHOHC≡), 1.91 (1H, ddd, *J* 14.5, 5.9, 2.7, *H*CHCHOHC≡), 1.75 (1H, dt, *J* 13.0, 2.7, HC*H*CHOPh), 1.69-1.60 (1H, m, *H*CHCHOPh overlap with CH_3), 1.65 (3H, s, CH_3), 1.53 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 142.0, 131.7, 128.5, 128.4, 128.3, 127.8, 125.9, 122.8, 99.4, 89.6, 85.1, 71.6, 67.8, 61.3, 42.1, 39.0, 30.3, 19.9.*m/z* (ESI-MS) 359.1 $(M+Na)^+$.

Compound **137**. This compound is novel.



(*S*,*S*)-**c2** (1.5 mg, 2.5 × 10^{-3} mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture (20 mg) and ketone **135** (11.5 mg, 0.034 mmol) in degassed CH_2Cl_2 (0.3 cm^3) was injected under a nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed then the reaction was quenched by addition of sat $NaHCO_3$ (0.5 cm^3), extracted with CH_2Cl_2 (3 × 6 cm^3) and the combined organic phase was dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=6:1-4:1) to afford the chiral alcohol as colourless oil (11.5 mg, 0.034 mmol, 99%, dr 37/1). $[\alpha]_D^{26}$+17.1(c 0.9 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.46-7.25 (10H, m, 2 × Ph), 4.94 (1H, dd, *J* 11.6, 2.4, *H*CPh), 4.85-4.81 (1H, t, *J* 6.6, CHC≡), 4.42-4.33 (1H, m, CH), 2.92 (1H, br, OH), 2.15-2.07 (1H, m, HC*H*CHOHC≡), 1.92 (1H, ddd, *J* 13.9, 5.8, 3.4, *H*CHCHOHC≡), 1.75 (1H, dt, *J* 13.1, 2.5, HC*H*CHOHPh), 1.67-1.56 (1H, m, *H*CHCHOHPh overlap with CH_3), 1.60 (3H, s, CH_3), 1.52 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 142.0, 131.7, 128.5, 128.4, 128.3, 127.7, 125.9, 122.7, 99.4, 89.5, 84.8, 71.5, 68.5, 61.6, 43.8, 39.2, 30.3, 19.9. *m/z* (ESI-MS) 359.1 $(M+Na)^+$.

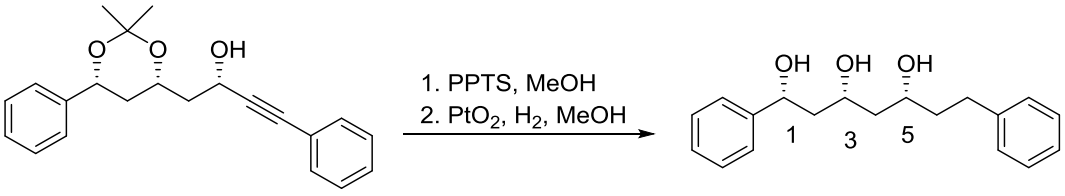
Yashabushitriol 129. This compound is known but not fully characterized.[115]



Alcohol (45.2 mg, 0.135 mmol) and PPTS (18 mg, 0.072 mmol) were dissolved in MeOH (3 cm^3) and the resulting solution was stirred overnight. MeOH was removed and the

residue was passed through a short silica gel column (eluent pure EtOAc) and concentrated. PtO_2 powder (2.0 mg, 8.8×10^{-3} mmol) was added followed by MeOH (3 cm^3). The mixture was degassed once and stirred vigorously under a 1 atm H_2 atmosphere for 30 min. The catalyst was removed by filtration and the solid residue was rinsed with MeOH (20 cm^3). The eluent was concentrated and purified by silica gel column chromatography (eluent hexane/EtOAc=2:1-1:2) to afford yashabushitriol **129** (34.6 mg, 0.115 mmol, 86% for 2 steps). MP 87 °C; $[\alpha]_D^{25}$+ 25.0(c 1.4 in $CHCl_3$); (lit MP 88.5-90 °C; $[\alpha]_D$+ 29.5 (in $CHCl_3$)); (found (ESI): M^+ + Na, 323.1618. $C_{19}H_{24}O_3$ requires M, 323.1617); ν_{max} 3324, 2914, 1105, 1059, 1028, 749, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.15 (10H, m, 2 × Ph), 4.98 (2H, dt, *J* 10.4 2.1, H-1), 4.38-4.31 (1H, m, H-3), 4.04-3.96 (2H, m, H-5 and OH), 3.13-3.15 (1H, br, OH), 2.80 (1H, ddd, *J* 13.7 9.0 5.9, H-7), 2.73 (1H, d, *J* 4.2, OH), 2.66 (1H, ddd, *J* 13.7 8.4 6.4, H-7), 2.02 (1H, dt, *J* 14.5 10.3, H-2), 1.93-1.83 (1H, m, H-6), 1.81-1.78 (1H, m, H-6), 1.73-1.67 (3H, m, H-4, H-2); δ_C (100 MHz, $CDCl_3$) 144.3, 142.0, 128.6, 128.5, 128.4, 127.7, 126.9, 125.7, 75.4, 70.4, 68.6, 45.1, 42.8, 39.2, 32.1. *m/z* (ESI-MS) 323.1 $(M+Na)^+$.

5-*epi*-**Yashabushitriol** 5-*epi*-**129.** This compound is novel.

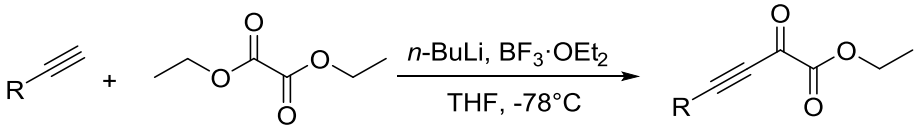


Alcohol (17.0 mg, 0.051 mmol) and PPTS (12 mg) was dissolved MeOH (2 cm^3) and the resulting solution was stirred overnight. MeOH was removed and the residue was passed through a short silica gel column (eluent pure EtOAc) and concentrated. PtO_2 (0.7 mg, 3.1×10^{-3} mmol) was added followed by MeOH (1 cm^3), the mixture was degassed once and stirred vigorously for 30 min under a 1 atm H_2 atmosphere.

The catalyst was removed by filtration and the solid residue was rinsed with MeOH. The eluent was concentrated and purified by silica gel column chromatography (eluent hexane/EtOAc=2:1-1:2) to afford 5-*epi*-Yashabushitriol 5-*epi*-**129** (11.2 mg, 0.037 mmol, 74%). $[\alpha]_D^{25}$+ 32.6 (c 0.5 in $CHCl_3$); ν_{max} 3316, 2922, 1058, 1028, 749, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.15 (10H, m, 2 × Ph), 4.94 (1H, dd, *J* 10.2, 2.6, H-1), 4.36 (1H, br, OH), 4.20 (1H, tt, *J* 9.7, 2.2, H-3), 3.96-3.88 (1H, m, H-5), 3.36 (1H, br, OH), 3.21(1H, br, OH), 2.79-2.59 (2H, m, H-7), 1.95-1.52 (6H, m, H-2, H-4, H-6); δ_C (100 MHz, $CDCl_3$) 144.3, 141.9, 128.6, 128.5, 128.4, 127.7, 125.9, 125.7, 75.3, 73.5, 72.2, 46.0, 43.5, 39.7, 31.7. *m/z* (ESI-MS) 323.1 $(M+Na)^+$.

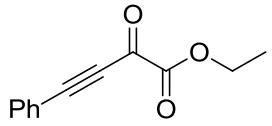
3.8. Synthesis of Acetylenic α-Keto Esters.

General Procedure



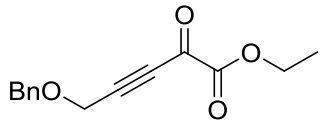
To a solution of acetylene (7.5 mmol) in anhydrous THF (6 cm^3) at -78 °C, *n*-BuLi (1.6 M in hexane, 4.7 cm^3, 7.5 mmol) was added over 3 min. The mixture was stirred at -78 °C for 1h then diethyl oxalate (1.46 g in 8 cm^3 THF, 10.0 mmol) was added dropwise over 3 min followed by $BF_3{\cdot}OEt_2$ (1.1 cm^3, 8.2 mmol). After 30 min the reaction was quenched by sat NH_4Cl (8 cm^3), extracted with EtOAc (2 × 15 cm^3) and dried over anhydrous $MgSO_4$. After concentration and removal of excess diethyl oxalate under reduced pressure, the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=15:1-10:1).

2-Oxo-4-phenyl-3-butynoic acid, ethyl ester 138. This compound is known and has been fully characterized.[175]



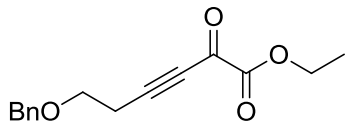
This compound was prepared following the general procedure above using phenylacetylene (765 mg, 7.5 mmol), *n*-BuLi (4.7 cm^3, 7.5 mmol), diethyl oxalate (1.46 g, 10.0 mmol) and $BF_3{\cdot}OEt_2$ (1.1 cm^3, 8.2 mmol). The product was isolated as a yellow oil (1.15 g, 5.7 mmol, 76%). δ_H (400 MHz, $CDCl_3$) 7.71-7.66 (2H, m, Ph), 7.55-7.51 (1H, m, Ph), 7.44-7.41 (2H, m, Ph), 4.41 (2H, q, *J* 7.1, CH_2), 1.43 (3H, t, *J* 7.1, CH_3); δ_C (100 MHz, $CDCl_3$) 169.6, 155.2, 133.8, 131.9, 128.8, 119.1, 98.0, 87.2, 63.3, 14.0.

5-Benzyloxy-2-oxo-3-pentynoic acid, ethyl ester 139. This compound is novel.



This compound was prepared following the general procedure above using acetylene (548 mg, 3.75 mmol), *n*-BuLi (2.40 cm^3, 3.85 mmol), diethyl oxalate (730 mg, 5.0 mmol) and $BF_3{\cdot}OEt_2$ (0.55 cm^3, 4.1 mmol). The product was isolated as yellow oil (737 mg, 3.0 mmol, 80%). (found (ESI): M^+ + Na, 269.0784; $C_{14}H_{14}O_4$ requires M, 269.0784); ν_{max} 2212, 1740, 1686, 1265, 1143, 739, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40-7.31 (5H, m, Ph), 4.67 (2H, s, PhC*H*$_2$), 4.41 (2H, s, $CH_2C{\equiv}$), 4.38 (2H, q, *J* 7.1, CH_2), 1.40 (3H, t, *J* 7.1, CH_3); δ_C (100 MHz, $CDCl_3$) 169.1, 158.7, 136.6, 128.6, 128.3, 128.2, 95.3, 84.2, 72.1, 63.4, 56.9, 13.9. *m/z* (EI-MS) 269.0 $(M+Na)^+$.

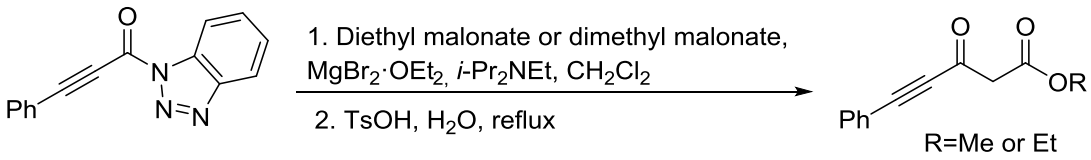
6-Benzyloxy-2-oxo-3-hexynoic acid, ethyl ester 140. This compound is novel.



This compound was prepared following the general procedure above using acetylene (600 mg, 3.75 mmol), *n*-BuLi (2.40 cm^3, 3.85 mmol), diethyl oxalate (730 mg, 5.0 mmol) and $BF_3{\cdot}OEt_2$ (0.55 cm^3, 4.1 mmol). The product was isolated as a colourless oil (820 mg, 3.20 mmol, 84%). (found (ESI): M^+ + H, 261.1121; $C_{15}H_{16}O_4$ requires M, 261.1121); ν_{max} 2213, 1738, 1680, 1156, 1096, 1017, 698, 650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35-7.28 (5H, m, Ph), 4.57 (2H, s, PhC*H*$_2$), 4.35 (2H, q, *J* 7.1, $COOCH_2$), 3.68 (2H, t, *J* 6.7, BnOC*H*$_2$), 2.78 (2H, t, *J* 6.7, $CH_2C{\equiv}$), 1.37 (3H, t, *J* 7.1, CH_3); δ_C (100 MHz, $CDCl_3$) 169.6, 159.2, 137.7, 128.5, 127.9, 127.7, 98.8, 80.2, 73.2, 66.8, 63.2, 21.1, 14.0. *m/z* (EI-MS) 283.1 $(M+Na)^+$.

3.9. Synthesis of Propargylic β-Keto Esters, Propargylic β-Keto Thioesters and Propargylic α-Methyl-β-keto Esters.

General Procedure [1] Claisen-type Condensation:



3-Oxo-5-phenyl-4-pentynethioic acid, methyl ester 143. This compound is known but not fully characterized.[176]

Dimethyl malonate (1.58 g, 12.0 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole **95** (2.47 g, 10.0 mmol), anhydrous $MgBr_2{\cdot}OEt_2$ powder (5.16 g, 20.0 mmol) was added to a flask and CH_2Cl_2 (30 cm^3) was added. The suspension was stirred at rt for 2 h then *i*-Pr_2NEt (3.87 g, 30.0 mmol) was added dropwise. A clear orange coloured solution was formed immediately and the solution was allowed to stir at rt for 0.5 h. Sat NH_4Cl (15 cm^3) was added followed by aqueous HCl (10%, 15 cm^3) and stirring was continued for 5 min. After a clear solution was formed the aqueous layer was extracted with CH_2Cl_2 (2 × 50

cm^3) and the combined organic extract was dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the crude product was semi-purified by a short silica gel column (eluent hexane/EtOAc= 12/1) to afford a mixture of Claison condensation adduct and dimethyl malonate.

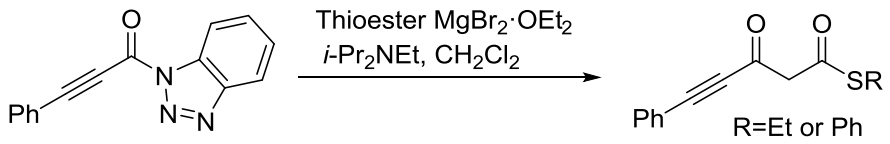
$TsOH \cdot H_2O$ (270 mg) and water (80 cm^3) was added to the aforementioned mixture and the resulting solution was refluxed for 6 h. The aqueous phase was extracted with Et_2O (3 × 40 cm^3) and the combined organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by a silica gel column (eluent hexane/EtOAc= 20/1-15/1) to afford product **143** as a colourless oil (1.37 g, 6.78 mmol, 68% for two steps, enol/β-keto=1.9/1). δ_H (400 MHz, $CDCl_3$) 11.87 (0.27H, s, OH), 7.62-7.34 (5H, m, Ph), 5.47 (0.27H, s, =CH), 3.80, 3.79 (3H, s, OCH_3), 3.71 (1.32H, s, CH_2).

3-Oxo-5-phenyl-4-pentynethioic acid, ethyl ester 144. This compound is known and has been fully characterized.[177]

Diethyl malonate (96 mg, 0.6 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole **95** (123 mg, 0.5 mmol), anhydrous $MgBr_2 \cdot OEt_2$ powder (258 mg, 1.0 mmol) was added to a flask and CH_2Cl_2 (2.5 cm^3) was added. The suspension was stirred at rt for 2 h then *i*-Pr_2NEt (194 mg, 1.5 mmol) was added dropwise. A clear orange colour solution was formed immediately and the solution was allowed to stir at rt for 1 h. Sat NH_4Cl (1.5 cm^3) was added followed by aqueous HCl (10%, 1.0 cm^3) and stirring was continued for 5 min. After a clear solution was formed, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 cm^3) the combined organic extract was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was semi-purified by a short silica gel

column (eluent hexane/EtOAc= 15/1) to afford a mixture of Claisen adduct and diethyl malonate.

$TsOH \cdot H_2O$ (20 mg) and water (6.0 cm^3) was added to the aforementioned mixture and the resulting solution was refluxed for 6 h. The aqueous phase was extracted with Et_2O (3 × 10 cm^3) and the combined organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by a silica gel column (eluent hexane/EtOAc= 15/1) to afford the product **144** as colourless oil (71 mg, 0.33 mmol, 66% for two steps). ν_{max} 2983, 2203, 1739, 1671, 1613, 1207, 1029, 756, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.98 (0.32H, s, OH), 7.58-7.32 (5H, m, Ph), 5.45 (0.32H, s, =CH), 4.27-4.20 (2H, m, $COOCH_2$), 3.69 (1.27H, s, CH_2), 1.32-1.27 (3H, m, CH_3); δ_C (100 MHz, $CDCl_3$) 178.8, 172.2, 166.1, 155.3, 133.3, 133.1, 132.2, 130.2, 130.8, 129.9, 128.7, 128.6, 128.5, 120.8, 119.5, 97.2, 93.4, 87.3, 83.4, 61.7, 60.7, 51.4, 50.6, 14.2, 14.1; *m/z* (EI-MS) 239.1 $(M+Na)^+$.



Thioester (2.0 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (2.0 mmol), anhydrous $MgBr_2 \cdot OEt_2$ powder (1.54 g, 6.0 mmol) were combined in a flask and CH_2Cl_2 (8.0 cm^3) was added. The suspension was stirred at rt for 2 h then *i*-Pr_2NEt (257 g, 2.0 mmol) was added dropwise. The solution was allowed to stir at rt for 0.5 h. Sat NH_4Cl (4 cm^3) was added follow by aqueous HCl (10%, 4 cm^3) and stirring was continued for 5 min. After a clear solution was formed the aqueous layer was extracted with CH_2Cl_2 (2 × 30 cm^3) and the combined organic extract was dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the crude product was purified by silica gel column (eluent hexane/EtOAc= 20/1-15/1) to afford pure product.

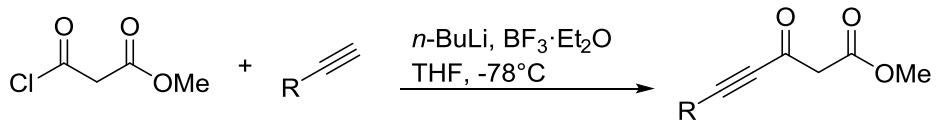
3-Oxo-5-phenyl-4-pentynethioic acid, S-ethyl ester 142. This compound is novel.

This compound was prepared following the general procedure above using S-ethyl thioacetate (52 mg, 0.5 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole **95** (124 mg, 0.5 mmol), anhydrous $MgBr_2 \cdot OEt_2$ powder (387 mg, 1.5 mmol) and *i*-Pr_2NEt (257 mg, 2.0 mmol). The product **142** was isolated as colourless oil (90 mg, 0.39 mmol, 78%, enol/β-keto=1.9/1). (found (ESI): M^+ + Na, 255.0450. $C_{13}H_{12}O_2S$ requires M, 255.0455); ν_{max} 2931, 2972, 2003, 1706, 1666, 1602, 1587, 1366, 1284, 1076, 865, 754, 686 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 12.53 (0.65H, s, OH), 7.59-7.35 (5H, m, Ph), 5.84 (0.65H, s, =CH), 3.89 (0.69H, s, CH_2), 2.97 (2H, q, *J* 7.4, OCH_2), 1.33-1.27 (3H, m, CH_3); δ_C (100 MHz, $CDCl_3$) 195.1, 178.2, 152.6, 133.3, 130.0, 132.3, 131.3, 130.6, 130.1, 128.7, 128.6, 120.7, 119.4, 106.3, 94.1, 83.3, 62.1, 59.4, 24.2, 23.1, 14.7, 14.1; *m/z* (EI-MS) 250.0 $(M+Na)^+$.

3-Oxo-5-phenyl-4-pentynethioic acid, S-phenyl ester 141. This compound is novel.

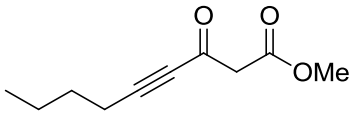
This compound was prepared following the general procedure above using S-phenyl thioacetate (304 mg, 2.0 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole **95** (500 mg, 2.0 mmol), anhydrous $MgBr_2 \cdot OEt_2$ powder (1.54 g, 6.0 mmol) and *i*-Pr_2NEt (1.04 g, 8.0 mmol). The product **141** was isolated as a white solid (500 mg, 1.79 mmol, 88%, enol/β-keto=2.0/1). MP 52 °C; (found (ESI): M^+ + Na, 303.0449. $C_{17}H_{12}O_2S$ requires M, 303.0455); δ_H (400 MHz, $CDCl_3$) 12.29 (0.67H, s, OH), 7.48-7.24 (10H, m, 2 × Ph), 5.80 (0.67H, s, =CH), 3.87 (0.68H, s, CH_2); δ_C (100 MHz, $CDCl_3$) 193.8, 177.9, 153.9, 135.0, 134.5, 133.4, 132.5, 131.4, 130.3, 130.0, 129.5, 129.4, 128.8, 128.7, 126.6, 120.5, 105.0, 94.9, 83.3, 58.9; *m/z* (EI-MS) 303.0 $(M+Na)^+$.

General Procedure [2] Condensation with Acid Chlorides:



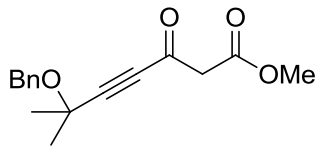
To a solution of alkyne (8.6 mmol) in anhydrous THF (12 cm^3) at -78 °C, *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol) was added via a syringe in 3 min. The mixture was stirred at the same temperature for 60 min then $BF_3{\cdot}Et_2O$ (1.1 cm^3, 8.5 mmol) was injected, and after 10 min malonic acid chloride monomethyl ester (495 mg, 3.63 mmol) in THF (1 cm^3) was added. The mixture was stirred for 2 h then was quenched by sat NH_4Cl (5 cm^3) and water (5 cm^3), extracted with Et_2O (3 × 20 cm^3) and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=20:1-15:1) to afford the pure product.

3-Oxo-4-nonynoic acid, methyl ester 161. This compound is novel.



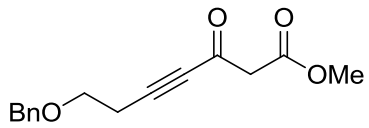
This compound was prepared following the general procedure above using 1-hexyne (705 mg, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}Et_2O$ (1.1 cm^3, 8.5 mmol) and malonic acid chloride monomethyl ester (495 mg, 3.63 mmol). The product was isolated as a colourless oil (320 mg, 1.75 mmol, 48%). (found (ESI): M^+ + Na, 205.0837. $C_{10}H_{14}O_3$ requires M, 205.0840); ν_{max} 2958, 2935, 2213, 1746, 1676, 1611, 1441, 1245, 1169, 1142, 805 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.81 (0.23H, s, OH), 5.29 (0.23H, s, =CH), 3.76 (major), 3.75 (minor), (3H, s, OCH_3), 3.58 (1.42H, s, $COCH_2$), 2.41-2.35 (2H, m, $\equiv CCH_2$), 1.61-1.54 (2H, m, CH_2), 1.48-1.39 (2H, m, CH_2), 0.93 (3H, t, *J* 7.3, CH_3); δ_C (100 MHz, $CDCl_3$) 178.7, 172.6, 166.6, 165.9, 97.1, 96.4, 95.8, 80.3, 52.5, 51.5, 51.1, 29.9, 29.5, 21.9, 18.9, 18.7, 13.4; *m/z* (EI-MS) 205.1 $(M+Na)^+$.

3-Oxo-6-benzyloxy-6 methyl-4-heptynoic acid, methyl ester 160. This compound is novel.



This compound was prepared following the general procedure above using alkyne (1.36 g, 7.9 mmol), *n*-BuLi (1.6 M in hexane, 4.6 cm^3, 7.4 mmol), $BF_3{\cdot}Et_2O$ (1.01 cm^3, 7.8 mmol) and malonic acid chloride monomethyl ester (390 mg, 2.8 mmol). The product was isolated as a colourless oil (313 mg, 1.14 mmol, 40%). (found (ESI): M^+ + Na, 297.1097. $C_{16}H_{18}O_4$ requires M, 297.1102); ν_{max} 2989, 2954, 2220, 1748, 1610, 1443, 1382, 1214, 1156, 805, 734, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.79 (0.41H, s, OH), 7.39-7.26 (5H, m, Ph), 5.35 (0.41H, s, =CH), 4.63 (major), 4.62 (minor), (2H, s, PhC*H*$_2$), 3.73 (major), 3.76 (minor), (3H, s, $COOCH_3$), 3.58 (1.04H, s, $COCH_2$), 1.60 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 178.4, 154.9, 138.5, 138.2, 128.44, 128.39, 127.74, 127.67, 127.57, 97.0, 96.1, 82.7, 78.8, 70.8, 70.6, 67.1, 67.0, 52.6, 51.7, 51.1, 28.4, 28.1; *m/z* (EI-MS) 297.1 $(M+Na)^+$.

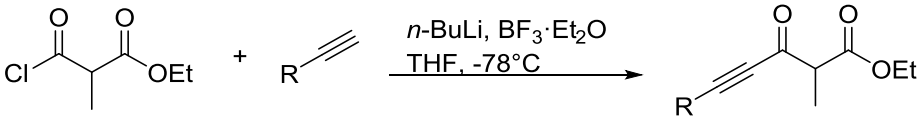
3-Oxo-7-benzyloxy-4-heptynoic acid, methyl ester 162. This compound is novel.



This compound was prepared following the general procedure above using alkyne (963 mg, 6.0 mmol), *n*-BuLi (1.6 M in hexane, 3.5 cm^3, 5.6 mmol), $BF_3{\cdot}Et_2O$ (0.77 cm^3, 6.0 mmol) and malonic acid chloride monomethyl ester (300 mg, 2.2 mmol). The product was isolated as a colourless oil (230 mg, 0.88 mmol, 45%). (found (ESI): M^+ + Na, 283.0941.

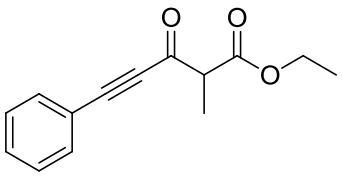
$C_{15}H_{16}O_4$ requires M, 283.0946); ν_{max} 2869, 2217, 1743, 1676, 1250, 1099, 737, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.80 (0.21H, s, OH), 7.37-7.26 (5H, m, Ph), 5.27 (0.21H, s, =CH), 4.53 (major), 4.54 (minor), (2H, s, PhC*H*$_2$), 3.72 (major), 3.73 (minor), (3H, s, OCH_3), 3.62 (2H, t, *J* 6.7, BnOC*H*$_2$), 3.57 (1.33H, s, $COCH_2$), 2.67 (2H, t, *J* 6.7, $\equiv CCH_2$); δ_C (100 MHz, $CDCl_3$) 178.6, 172.6, 166.6, 155.5, 137.7, 128.5, 127.9, 127.7, 96.3, 93.5, 92.9, 80.9, 76.3, 73.1, 73.0, 67.3, 67.0, 52.5, 51.6, 51.0, 20.8, 20.6; *m/z* (EI-MS) 283.1 $(M+Na)^+$.

General Procedure



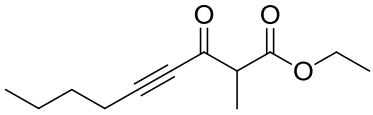
To a solution of alkyne (8.6 mmol) in anhydrous THF (12 cm^3) at -78 °C *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol) was added via a syringe in 3 min. The mixture was stirred at the same temperature for 10 min then $BF_3{\cdot}Et_2O$ (1.1 cm^3, 8.5 mmol) was injected. After 10 min, 3-chloro-2-methyl-3-oxo-propanoic acid, ethyl ester (510 mg, 3.10 mmol) in THF (1 cm^3) was added in one portion. The mixture was stirred for 1.5 h then was quenched by sat NH_4Cl (5 cm^3) and water (5 cm^3), extracted with Et_2O (2 × 20 cm^3), dried over anhydrous $MgSO_4$. After concentration under reduced pressure the crude product was purified by silica gel column chromatography (eluent hexane/DCM=10:1-10:3) to afford the pure product.

2-Methyl-3-oxo-5-phenyl-4-pentynethioic acid, ethyl ester 163. This compound is novel.



This compound was prepared following the general procedure above using phenylacetylene (877 mg, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3 \cdot Et_2O$ (1.1 cm^3, 8.5 mmol) and freshly prepared 3-chloro-2-methyl-3-oxo-propanoic acid, ethyl ester (510 mg, 3.10 mmol). The product was isolated as light yellow crystals (551 mg, 2.40 mmol, 77%). MP 59 °C; (found (ESI): M^+ + Na, 253.0835. $C_{14}H_{14}O_3$ requires M, 253.0840); ν_{max} 2994, 2931, 2905, 2211, 1631, 1604, 1379, 1276, 1188, 1061, 789, 753, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 12.21 (0.74H, s, OH), 7.60-7.51 (2H, m, Ph), 7.46-7.33 (3H, m, Ph), 4.28-4.21 (2H, m, $COOCH_2$), 3.68 (0.26H, q, *J* 7.2, CH), 2.00 (2.22H, s, $=CCH_3$), 1.50 (0.78H, d, *J* 7.2, $CHCH_3$), 1.33 (2.26H, t, *J* 7.1, $COOCH_2CH_3$), 1.28 (0.74H, t, *J* 7.1, $COOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 128.9, 173.0, 152.0, 133.2, 132.0, 131.1, 129.7, 128.7, 128.5, 121.3, 119.6, 104.2, 97.7, 96.3, 86.4, 83.0, 61.6, 61.0, 55.0, 14.2, 14.1, 13.2, 12.9; *m/z* (EI-MS) 253.1 $(M+Na)^+$.

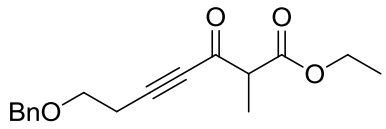
2-Methyl-3-oxo-4-nonynoic acid, ethyl ester 165. This compound is novel.



This compound was prepared following the general procedure above using 1-hexyne (706 mg, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3 \cdot Et_2O$ (1.1 cm^3, 8.5 mmol) and freshly prepared 3-chloro-2-methyl-3-oxo-propanoic acid, ethyl ester (510 mg, 3.10 mmol). The product was isolated as alight yellow oil (538 mg, 2.56 mmol, 82%). (found (ESI): M^+ + Na, 233.1148. $C_{12}H_{18}O_3$ requires M, 233.1153); ν_{max} 2961, 2935, 2211, 1741, 1678, 1644, 1600, 1334, 1243, 1121cm^{-1}; δ_H (400 MHz, $CDCl_3$) 12.15 (0.52H, s, OH), 4.24 (q, *J* 7.1) and 4.21 (qd, *J* 7.1 2.0) (total 2H, $COOCH_2$), 3.54 (0.34H, q, *J* 7.2, CH), 2.44 (1.29H, t, *J* 7.1, $CH_2C\equiv$), 2.39 (0.71H, t, *J* 7.1, $CH_2C\equiv$), 1.89 (1.72H, s, $=CCH_3$), 1.62-1.53 (2H, m, CH_2), 1.50-1.41 (2H, m, CH_2), 1.42 (1.17H, d, *J* 7.2, $CHCH_3$), 1.32 (t, *J*

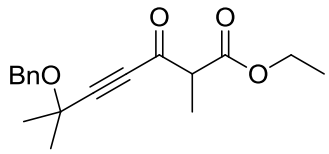
7.1, $COOCH_2CH_3$) and 1.28 (t, *J* 7.1) (total 3H, $COOCH_2CH_3$), 0.934 (t, *J* 7.3) and 0.928 (t, *J* 7.3) (total 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 173.1, 169.7, 152.4, 103.0, 100.3, 97.1, 79.4, 74.9, 61.4, 60.8, 54.9, 30.1, 29.6, 21.94, 21.89, 19.1, 18.7, 14.2 14.0, 13.5 13.4, 12.9, 12.8; *m/z* (EI-MS) 233.1 $(M+Na)^+$.

2-Methyl-3-oxo-7-benzyloxy-4-heptynoic acid, ethyl ester 166. This compound is novel.



This compound was prepared following the general procedure above using acetylene (640 mg, mmol), *n*-BuLi (1.6 M in hexane, 2.32 cm^3, 3.71 mmol), $BF_3{\cdot}Et_2O$ (0.50 cm^3, 3.9 mmol) and freshly prepared 3-chloro-2-methyl-3-oxo-propanoic acid, ethyl ester (237 mg, 1.44 mmol). The product was isolated as colourless oil (298 mg, 1.03 mmol, 72%). (found (ESI): M^+ + Na, 311.1254. $C_{17}H_{20}O_4$ requires M, 311.1259); ν_{max} 2865, 2225, 1738, 1643, 1600, 1374, 1334, 1243, 1119, 1096, 1025, 804, 734, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 12.05 (0.68H, s, OH), 7.35-7.18 (5H, m, Ph), 4.49 (major), 4.47(minor) (2H total, s, $PhCH_2O$), 4.19-4.06 (2H, m, $COOCH_2$), 3.61-3.40 (2.53H, m, OCH_2CH_2, C*H*), 2.67 (major, *J* 6.9) 2.61(minor, *J* 6.8) (2H, t, $OCH_2CH_2C{\equiv}$), 1.81 (2.33H, s, $=CCH_3$), 1.37-1.36 (0.87H, d, *J* 7.2, $CHCH_3$), 1.26-1.11 (3H, m, $COOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 173.1, 152.0, 137.9, 128.6, 128.5, 128.3, 128.1, 127.8, 127.7, 103.5, 96.7, 75.8, 73.1, 67.7, 67.1, 67.0, 61.5, 61.4, 60.9, 54.8, 46.2, 21.0, 20.6, 14.2, 14.0, 13.6, 13.0; *m/z* (EI-MS) 311.1 $(M+Na)^+$.

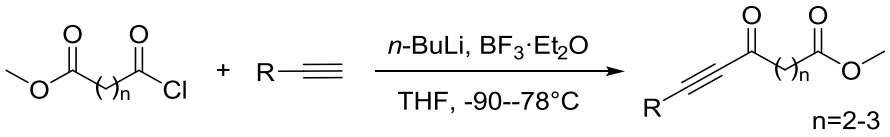
2-Methyl-3-oxo-6-benzyloxy-6-methyl-4-heptynoic acid, ethyl ester 164. This compound is novel.



This compound was prepared following the general procedure above using acetylene (1.50 g, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}OEt_2$ (1.1 cm^3, 8.5 mmol) and freshly prepared 3-chloro-2-methyl-3-oxo-propanoic acid, ethyl ester (510 mg, 3.10 mmol). The product was isolated as a colourless oil (864 mg, 2.86 mmol, 92%). (found (ESI): M^+ + Na, 325.1410. $C_{18}H_{22}O_4$ requires M, 325.1415); ν_{max} 2986, 2218, 1735, 1643, 1600, 1374, 1333, 1207, 1155, 1086, 735, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 12.06 (0.71H, s, OH), 7.12-7.39 (5H, m, Ph), 4.58 (major), 4.54 (minor) (2H, s, PhCH_2O), 4.19-4.05 (2H, m, $COOCH_2$), 3.50 (q, *J* 7.2) and 3.35 (q, *J* 7.3) (0.22H total, CH), 1.83 (2.28H, s, $=CCH_3$), 1.54 (6H, s, 2 × CH_3), 1.52 (masked by other peaks CHCH_3), 1.35 (0.80, t, *J* 7.0, $COOCH_2CH_3$), 1.24 (2.20H, t, *J* 7.1, $COOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 172.9, 151.5, 138.6, 128.4, 128.3, 127.8, 127.7, 127.6, 104.2, 100.3, 96.1, 86.9, 78.3, 71.0, 67.0, 61.6, 61.4, 61.0, 55.0, 46.2, 40.9, 30.5, 28.6, 28.2, 19.0, 14.2, 14.1, 13.1, 12.8; *m/z* (EI-MS) 325.1 $(M+Na)^+$.

3.10. Synthesis of Acetylenic γ-Keto Esters and δ-Keto Esters.

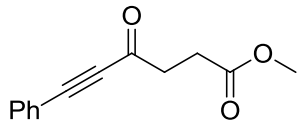
General Procedure [1] Preparation from Alkynyl Boranes:



To a solution of acetylene (7.5 mmol) in anhydrous THF (6 cm^3) at -78 °C, *n*-BuLi (1.6 M in hexane, 4.7 cm^3, 7.5 mmol) was added in 3 min. The mixture was stirred at 0 °C for 1 h after cooling to -78 °C, when $BF_3{\cdot}OEt_2$ (1.46 g in 8 cm^3 THF, 10.0 mmol) was added dropwise. After 10 min the mixture was cooled to -90 °C and 4-chloro-4-oxo-butanoic

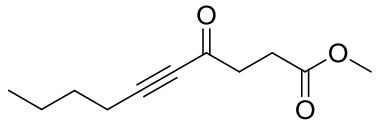
acid methyl ester (1.46 g in 2 cm^3 THF, 10.0 mmol) was added in one portion. The reaction was quenched by sat NH_4Cl (8 cm^3) and water (8 cm^3) after 2 h, extracted with Et_2O (2 × 30 cm^3), dried over anhydrous $MgSO_4$. After concentration under reduced pressure the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=15:1-8:1).

4-Oxo-6-phenyl-5-hexynoic acid methyl ester 176. This compound is novel.



This compound was prepared following the general procedure above using phenylactylene (1.63 g, 16 mmol), *n*-BuLi (1.6 M in hexane, 9.5 cm^3, 15.0 mmol), $BF_3{\cdot}Et_2O$ (2.0cm^3, 16.0 mmol) and 4-chloro-4-oxo-butanoic acid methyl ester (2.62 g, 17.4 mmol). The product was isolated as a colourless oil (1.61 g, 7.4 mmol, 49%). (found (ESI): M^+ + Na, 239.0682. $C_{13}H_{12}O_3$ requires M 239.0684); ν_{max} 2953, 2200, 1734, 1667, 1205, 1168, 1093, 758, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.60-7.56 (2H, m, Ph), 7.49-7.44 (1H, m, Ph), 7.41-7.36(2H, m, Ph), 3.71 (3H, s, $COOCH_3$), 3.03 (2H, t, *J* 6.7, CH_2),2.72 (2H, t, *J* 6.7, CH_2); δ_C (100 MHz, $CDCl_3$) 185.4, 172.5, 133.0, 130.8, 128.7, 119.8, 91.4, 87.4, 51.9, 40.0, 27.8; *m/z* (EI-MS) 239.1 $(M+Na)^+$.

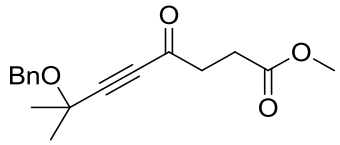
4-Oxo-5-decynoic acid, methyl ester 177. This compound is novel.



This compound was prepared following the general procedure above using 1-hexyne (705 mg, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}Et_2O$ (1.1cm^3, 8.5 mmol) and 4-chloro-4-oxo-butanoic acid methyl ester (1.57 g, 10.4 mmol). The product

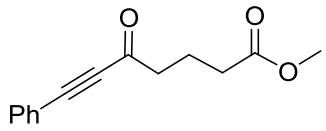
was isolated as a colourless oil (417 mg, 2.1 mmol, 27%). (found (ESI): M^+ + Na, 219.0992. $C_{11}H_{16}O_3$ requires M 219.0997); ν_{max} 2958, 2210, 1737, 1675, 1208, 1154 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, $COOCH_3$), 2.88 (2H, t, *J* 6.7, CH_2), 2.64 (2H, t, *J* 6.7, CH_2), 2.38 (2H, t, *J* 7.1, $CH_2C\equiv$), 1.63-1.51 (2H, m, CH_2), 1.51-1.35 (2H, m, CH_2), 0.93 (3H, t, *J* 7.2, CH_3); δ_C (100 MHz, $CDCl_3$) 185.5, 172.6, 95.1, 80.4, 51.8, 40.0, 29.6, 27.8, 21.9, 18.6, 13.4; *m/z* (EI-MS) 219.1 $(M+Na)^+$.

4-Oxo-7-benzyloxy-7-methyl-5-octynoic acid, methyl ester 178. This compound is novel.



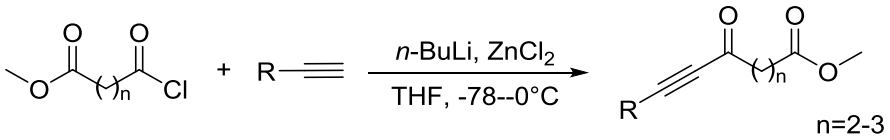
This compound was prepared following the general procedure above using alkyne (1.50 g, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}Et_2O$ (1.1cm^3, 8.5 mmol) and 4-chloro-4-oxo-butanoic acid methyl ester (1.57 g, 10.4 mmol). The product was isolated as a colourless oil (541 mg, 1.9 mmol, 22%). (found (ESI): M^+ + Na, 311.1254. $C_{17}H_{20}O_4$ requires M 311.1259); ν_{max} 3032, 2210, 1737, 1679, 1122, 736, 697cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.24 (5H, m, Ph), 4.62 (2H, s, PhCH_2), 3.68 (3H, s, $COOCH_3$), 2.89 (2H, t, *J* 7.6, CH_2), 2.63 (2H, t, *J* 7.6, CH_2), 1.59 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 185.1, 172.4, 138.4, 128.4, 127.7, 127.6, 94.2, 82.9, 70.6, 67.0, 51.9, 40.1, 28.2, 27.6; *m/z* (EI-MS) 311.1 $(M+Na)^+$.

5-Oxo-7-phenyl-6-heptynoic acid, methyl ester 180. This compound is known and has been fully characterized.[178]



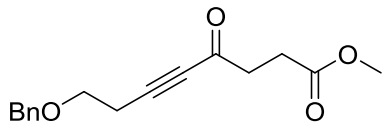
This compound was prepared following the general procedure above using phenylacetylene (326 mg, 3.2 mmol), *n*-BuLi (1.6 M in hexane, 1.9 cm^3, 3.0 mmol), $BF_3 \cdot Et_2O$ (454 mg, 0.4 cm^3, 3.2 mmol) and glutaric acid monomethyl ester chloride (526 mg, 3.2 mmol). The product was isolated as a colourless oil (300 mg, 1.3 mmol, 43%). (found (ESI): M^+ + Na, 253.0833. $C_{14}H_{14}O_3$ requires M 253.0840); ν_{max} 2952, 2199, 1733, 1667, 1197, 1168, 758, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.60-7.55 (2H, m, Ph), 7.49-7.43 (1H, m, Ph), 7.41-7.35 (2H, m, Ph), 3.69-3.66 (3H, m, $COOCH_3$), 2.82-2.73 (2H, m, $COCH_2$), 2.44-2.35 (2H, m, CH_2COO), 2.10-2.01 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 186.8, 173.3, 133.0, 130.8, 128.6, 119.8, 90.9, 87.7, 51.6, 43.3, 32.8, 19.1. *m/z* (EI-MS) 253.1 $(M+Na)^+$.

General Procedure [2] Preparation by Using Alkynylzinc Reagents:



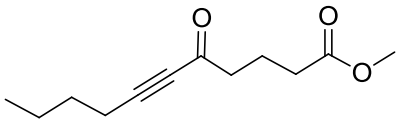
To a solution of acetylene (8.6 mmol) in anhydrous THF (20 cm^3) at -78 °C, *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol) was added in 3 min. The mixture was stirred at -78 °C for 1 h, anhydrous $ZnCl_2$ (1.90 g in 8 cm^3 THF, 14.0 mmol) was added and the mixture was warmed to 0 °C for 30 min then glutaric acid monomethyl ester chloride (987 mg, 6.0 mmol) was added in one portion. The reaction was stirred overnight and quenched by sat NH_4Cl (10 cm^3), water (10 cm^3), extracted with Et_2O (2 × 30 cm^3) and dried over anhydrous $MgSO_4$. After concentration under reduced pressure the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=15:1-8:1).

4-Oxo-8-benzyloxy-5-octynoic acid, methyl ester 179. This compound is novel.



This compound was prepared following the general procedure above using alkyne (674 mg, 4.3 mmol), *n*-BuLi (1.6 M in hexane, 2.5 cm^3, 4.0 mmol), anhydrous $ZnCl_2$ (950 mg, 7.0 mmol) and 4-chloro-4-oxo-butanoic acid methyl ester (451 mg, 3.0 mmol). The product was isolated as a colourless oil (204.9 mg, 0.75 mmol, 25%). (found (ESI): M^+ + Na, 297.1097. $C_{16}H_{18}O_4$ requires M 297.1102); ν_{max} 2952, 2864, 2213, 1734, 1674, 1208, 1155, 1100, 738, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.27 (5H, m, Ph), 4.56 (2H, s, PhC*H*$_2$), 3.68 (3H, s, $COOCH_3$), 3.64 (2H, t, *J* 6.8, BnOC*H*$_2$), 2.89 (2H, t, *J* 6.8, $COCH_2$), 2.69 (2H, t, *J* 6.8, $CH_2C\equiv$), 2.64 (2H, t, *J* 6.8, CH_2COO); δ_C (100 MHz, $CDCl_3$) 185.4, 172.6, 137.7, 128.5, 127.9, 127.7, 91.5, 81.0, 73.1, 67.1, 51.9, 40.0, 27.8, 20.5; *m/z* (EI-MS) 275.1 $(M+H)^+$.

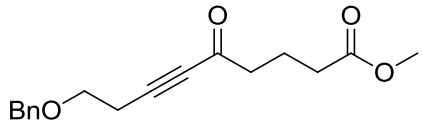
5-Oxo-6-undecynoic acid, methyl ester 181. This compound is known but not fully characterized.[179]



This compound was prepared following the general procedure above using 1-hexyne (1.42 g, 17.2 mmol), *n*-BuLi (1.6 M in hexane, 10.0 cm^3, 16.0 mmol), anhydrous $ZnCl_2$ (3.77 g, 28 mmol) and 4-chloro-4-oxo-butanoic acid methyl ester (1.97 g, 12.0 mmol). The product was isolated as a colourless oil (1.33 g, 6.3 mmol, 53%). (found (ESI): M^+ + Na, 233.1148. $C_{12}H_{18}O_3$ requires M 233.1153); ν_{max} 2958, 2210, 1736, 1671, 1196, 1161 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.60 (3H, s, $COOCH_3$), 2.54 (2H, t, *J* 7.2, $COCH_2$), 2.30 (2H, t, *J*

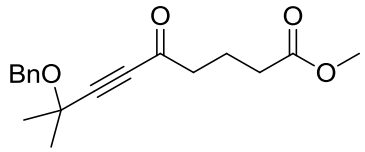
7.0, $CH_2C\equiv$), 2.29 (2H, t, *J* 7.2, CH_2), 1.94-1.86 (2H, m, CH_2CH_2COO), 1.53 (2H, m, CH_2), 1.46 (2H, m, CH_2), 0.86 (3H, t, *J* 7.3, CH_3); δ_C (100 MHz, $CDCl_3$) 187.0, 173.3, 94.6, 80.7, 51.5, 44.3, 32.8, 29.6, 21.9, 19.1, 18.5, 13.4. *m/z* (EI-MS) 233.1 $(M+Na)^+$.

5-Oxo-9-benzyloxy-6-nonynoic acid, methyl ester 183. This compound is novel.



This compound was prepared following the general procedure above using acetylene (1.50 g, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), anhydrous $ZnCl_2$ (1.90 g, 14.0 mmol) and 4-chloro-4-oxo-butanoic acid methyl ester (987 mg, 6.0 mmol). The product was isolated as a colourless oil (1.274 g, 4.4 mmol, 73%). (found (ESI): M^+ + Na, 311.1254. $C_{17}H_{20}O_4$ requires M 311.1259); ν_{max} 2952, 2866, 2214, 1733, 1671, 1199, 1162, 1099, 737, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.26 (2H, m, Ph), 4.62 (2H, s, $PhCH_2O$), 3.66 (3H, s, $COOCH_3$), 3.63 (2H, t, *J* 6.7, OCH_2), 2.66 (2H, t, *J* 6.7, $CH_2C\equiv$), 2.61 (2H, t, *J* 7.2, $COCH_2$), 2.35 (2H, t, *J* 7.2, CH_2COO), 2.00-1.92 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 186.9, 173.3, 137.8, 128.5, 127.8, 127.7, 91.1, 81.3, 73.1, 67.2, 51.6, 44.3, 32.8, 20.5, 19.0. *m/z* (EI-MS) 311.1 $(M+Na)^+$.

5-Oxo-8-benzyloxy-8-methyl-6-nonynoic acid, methyl ester 182. This compound is novel.

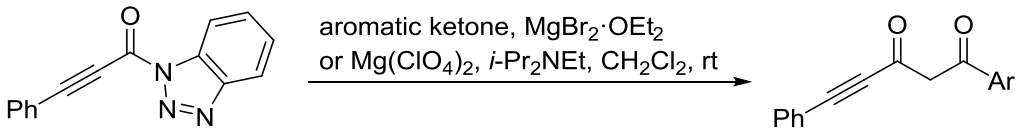


This compound was prepared following the general procedure above using acetylene (1.50 g, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), anhydrous $ZnCl_2$ (1.90 g,

14.0 mmol) and 4-chloro-4-oxo-butanoic acid methyl ester (987 mg, 6.0 mmol). The product was isolated as a colourless oil (884 mg, 2.90 mmol, 48%). (found (ESI): M^+ + Na, 325.1410. $C_{18}H_{22}O_4$ requires M 325.1415); ν_{max} 2987, 2952, 2213, 1734, 1676, 1156, 1049, 737, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.24 (5H, m, Ph), 4.62 (2H, s, PhCH_2O), 3.66 (3H, s, $COOCH_3$), 2.63 (2H, t, *J* 7.2, $COCH_2$), 2.36 (2H, t, *J* 7.2, CH_2COO), 2.00-1.93 (2H, m, CH_2), 1.60 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 186.5, 173.2, 138.4, 128.4, 127.63, 127.60, 93.8, 83.2, 70.6, 67.0, 51.7, 44.4, 32.7, 28.3, 19.0. *m/z* (EI-MS) 325.1 $(M+Na)^+$.

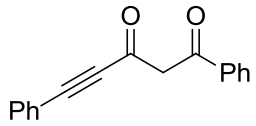
3.11. Synthesis of 4-Pentyne-1,3-diones.

General Procedure



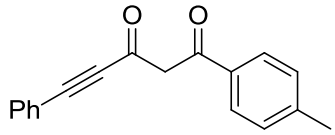
Aromatic ketone (0.37 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (0.38 mmol) and anhydrous $MgBr_2{\cdot}OEt_2$ powder [or anhydrous $Mg(ClO_4)_2$ powder] (0.76 mmol) was added to a flask and laboratory grade CH_2Cl_2 (1.5 cm^3) was added via a syringe. The suspension was stirred at rt for 3 h then *i*-Pr_2NEt (1.0 mmol) was added dropwise. A clean yellow solution was formed immediately and the solution was allowed to stir at rt for 5 h. Sat NH_4Cl (3 cm^3) was added follow by aqueous HCl (10 %, 1 cm^3) and stirring was continued for 5 min. After a clear solution has formed the aqueous layer was extracted with CH_2Cl_2 (2 x 5 cm^3) and the combined organic extract was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the yellow solid product was dissolved in the minimum amount of CH_2Cl_2 and purified by silica gel column chromatography [eluent hexane/ CH_2Cl_2/EtOAc= 10:1:0-10:1: (0.2-0.4)].

1,5-Diphenyl-4-pentyne-1,3-dione 192. This compound is known and has been fully characterized.[134]



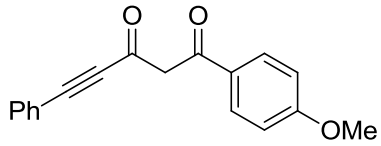
This compound was prepared following the general procedure above using acetophenone (873 mg, 7.4 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (1.84 g, 7.6 mmol), $MgBr_2 \cdot OEt_2$ (3.92 g, 15.2 mmol) and *i*-Pr_2NEt (2.51 g, 20.0 mmol). The product was isolated as described above as light yellow crystals (1.49 g, 6.0 mmol, 81%); δ_H (400 MHz, $CDCl_3$) 7.71-7.68 (2H, m, Ph), 7.38-7.31 (3H, m, Ph), 7.27-7.13 (5H, m, Ph), 6.29 (1H, s, =CH); δ_C (75 MHz, $CDCl_3$) 184.7, 169.7, 133.9, 132.3, 132.1, 129.8, 128.3, 128.2, 128.0, 126.7, 119.8, 100.7, 93.3, 85.5.

1-(4-Methylphenyl)-5-phenyl-4-pentyne-1,3-dione 193. This compound is known and has been fully characterized.[134]



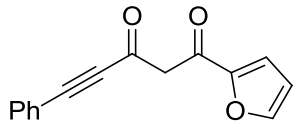
This compound was prepared following the general procedure above using *p*-methyl acetophenone (45.0 mg, 0.34 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (94.0 mg, 0.38 mmol), $Mg(ClO_4)_2$ (170.0 mg, 0.76 mmol) and *i*-Pr_2NEt (129.0 mg, 1.0 mmol). The product was isolated as described above as yellow crystals (60 mg, 0.23 mmol, 66%); δ_H (400 MHz, $CDCl_3$) 15.87 (1H, br, OH), 7.90-7.81 (2H, m, Ar), 7.64-7.58 (2H, m, Ar), 7.47-7.36 (3H, m, Ar), 7.31-7.25 (2H, m, Ar), 6.50 (1H, s, =CH), 2.42 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 185.7, 169.7, 143.9, 132.7, 131.9, 130.4, 129.5, 128.6, 127.4, 120.6, 101.1, 93.6, 86.2, 21.7.

1-(4-Methoxyphenyl)-5-phenyl-4-Pentyne-1,3-dione 194. This compound is known but not fully characterized.[180]



This compound was prepared following the general procedure above using *p*-methoxyl acetophenone (25.5 mg, 0.17 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (47.0 mg, 0.19 mmol), $Mg(ClO_4)_2$ (85.0 mg, 0.38 mmol) and *i*-Pr_2NEt (64.0 mg, 0.50 mmol). The product was isolated as described above as yellow crystals (34 mg, 0.12 mmol, 72%); δ_H (400 MHz, $CDCl_3$) 15.97 (1H, br, OH), 7.94-7.90 (2H, m, *p*-MeO*Ph*), 7.62-7.57 (2H, m, Ph), 7.47-7.36 (3H, m, Ph), 6.98-6.95 (2H, m, *p*-MeO*Ph*), 6.47 (1H, s, =CH), 3.88 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 185.9, 168.4, 163.7, 132.6, 130.3, 129.6, 128.6, 127.2, 120.6, 114.1, 100.8, 93.5, 86.0, 55.5.

1-(2-Furanyl)-5-phenyl-4-pentyne-1,3-dione 195. This compound is known but not fully characterized.[181]

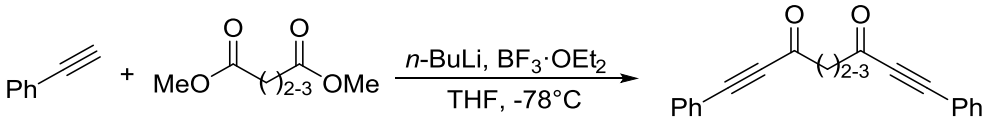


This compound was prepared following the general procedure above using 1-(2-furyl)ethanone (374 mg, 3.40 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (940 mg, 3.80 mmol), $Mg(ClO_4)_2$ (1.70 g, 7.6 mmol) and *i*-Pr_2NEt (1.28 g, 10.0 mmol). The product was isolated as described above as yellow crystals (491 mg, 2.06 mmol, 61%); δ_H (400 MHz, $CDCl_3$) 15.10 (1H, br, OH), 7.64-7.57 (3H, m, Ar), 7.62-7.57 (3H, m, Ph and 2-furyl), 7.47-7.36 (3H, m, Ph), 7.24 (1H, d, *J* 3.5, 2-furyl), 6.59 (1H, dd, *J* 3.5, 1.7, 2-

furyl), 6.44 (1H, s, =CH); δ_C (75 MHz, $CDCl_3$) 177.4, 166.2, 150.4, 146.8, 132.6, 130.4. 128.6, 120.5, 116.9, 112.9, 101.4, 94.5, 85.3.

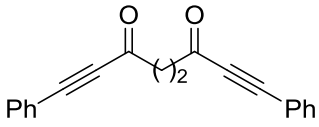
3.12. Synthesis of Propargylic 1,4-Diketones and 1,5-Diketones.

General Procedure [1] from Diesters:



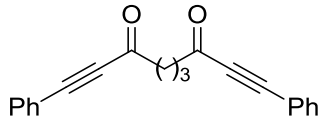
To a solution of acetylene (7.5 mmol) in anhydrous THF (6 cm^3) at -78 °C *n*-BuLi (1.6 M in hexane, 4.7 cm^3, 7.5 mmol) was added in 3 min. The mixture was stirred at -78 °C for 1 h and was added dropwise to a diester (2.5 mmol in 8 cm^3 THF) and $BF_3{\cdot}OEt_2$ (6.5 mmol) mixture at -78 °C. After 1 h, sat NH_4Cl (10 cm^3) was added and the mixture was extracted with diethyl ether (3 × 30 cm^3). The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=15:1).

1,8-Diphenyl-1,7-octadiyne-3,6-dione 197. This compound is known and has been fully characterized.[138]



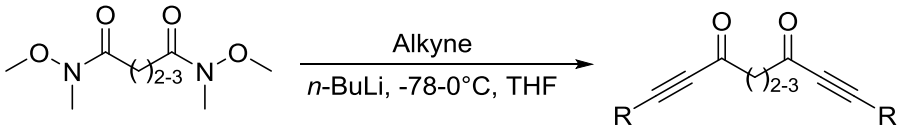
This compound was prepared following the general procedure above using phenylacetylene (1.76 g, 17.2 mmol), *n*-BuLi (10.0 cm^3, 16.0 mmol), dimethyl succinate (778 mg, 5.3 mmol) and $BF_3{\cdot}OEt_2$ (1.73 cm^3, 13.8 mmol). The product was isolated as a white solid (394 mg, 1.38 mmol, 26%). δ_H (400 MHz, $CDCl_3$) 7.60-7.57 (4H, m, 2 × Ph), 7.49-7.44 (2H, m, 2 × Ph), 7.41-7.37 (4H, m, 2 × Ph), 3.12 (4H, s, 2 × CH_2); δ_C (100 MHz, $CDCl_3$) 185.1, 133.1, 130.9, 128.7, 119.8, 91.7, 87.5, 34.0.

1,9-Diphenyl-1,8-nonadiyne-3,7-dione 198. This compound is known and has been fully characterized.[138]



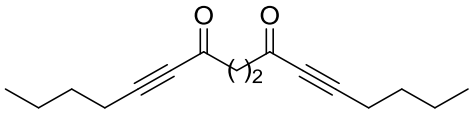
This compound was prepared following the general procedure above using phenylacetylene (0.88 g, 8.6 mmol), *n*-BuLi (5.0 cm^3, 8.0 mmol), dimethyl glutarate (457 mg, 2.86 mmol) and $BF_3 \cdot OEt_2$ (1.1 cm^3, 8.5 mmol). The product was isolated as white solid (148 mg, 0.49 mmol, 17%). δ_H (400 MHz, $CDCl_3$) 7.60-7.23 (10H, m, 2 × Ph), 2.71 (4H, t, *J* 7.2, 2 × CH_2CO), 2.12-2.05 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 186.9, 133.1, 130.8, 128.7, 119.8, 91.2, 87.7, 44.2, 18.3.

General Procedure [2] from Weinreb Diamides:



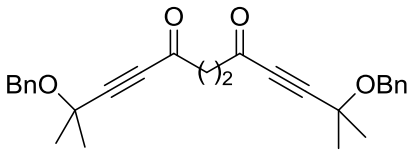
To a solution of acetylene (2.4 mmol) in anhydrous THF (10 cm^3) at -78 °C *n*-BuLi (1.6 M in hexane, 1.5 cm^3, 2.4 mmol) was added in 3 min. The mixture was stirred at -78 °C for 1 h and a Weinreb diamide (204 mg in 3 cm^3 THF, 1.0 mmol) solution was added dropwise. After 1h at -78 °C, the temperature was raised to -10 °C during 2 h and sat NH_4Cl (20 cm^3) and 2M HCl solution (5 cm^3) was added at -10 °C. The mixture was extracted with diethyl ether (3 × 20 cm^3) and combined organic phase was dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=12:1-8:1).

1,8-Dibutyl-1,7-octadiyne-3,6-dione 201. This compound is novel.



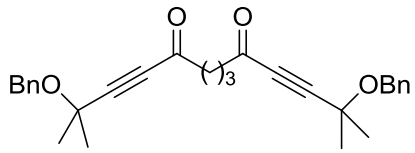
This compound was prepared following the general procedure above using Weinreb diamide (326 mg, 1.6 mmol), *n*-BuLi (3.0 cm^3, 4.8 mmol), 1-hexyne (417 mg, 2.4 mmol), and the product was isolated as described above as a colourless oil (361 mg, 1.47 mmol, 92%). (found (ESI): M^+ + Na, 269.1512. $C_{16}H_{22}O_2$ requires M, 269.1517); ν_{max} 2959, 2934, 2872, 2219, 1670, 1192, 1150 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.89 (4H, s, 2 × CH_2CO), 2.37 (4H, t, *J* 7.3, 2 × $CH_2C\equiv$), 1.61-1.53 (4H, m, 2 × $CH_2CH_2C\equiv$), 1.48-1.39 (4H, m, 2 × CH_2CH_3), 0.93 (6H, t, *J* 7.3, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 185.4, 95.2, 80.5, 38.9, 29.6, 21.9, 18.6, 13.5; *m/z* (EI-MS) 268.9 $(M+Na)^+$.

1,10-Dibenzyloxy-1,10-tetramethyl-2,8-octadiyne-4,7-dione 199. This compound is novel.



This compound was prepared following the general procedure above using Weinreb diamide (204 mg, 1.0 mmol), *n*-BuLi (1.5 cm^3, 2.4 mmol), alkyne (417 mg, 2.4 mmol), and the product was isolated as described above as a yellow oil (186 mg, 0.43 mmol, 43%). (found (ESI): M^+ + Na, 453.2036. $C_{28}H_{30}O_4$ requires M, 453.2041); ν_{max} 2987, 2210, 1675, 1235, 1157, 1113, 1047, 735, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.24 (10H, m, 2 × Ph), 4.62 (4H, s, 2 × CH_2O), 2.91 (4H, m, 2 × CH_2), 1.59 (12H, s, 4 × CH_3); δ_C (100 MHz, $CDCl_3$) 184.6, 183.3, 128.4, 127.67, 127.64, 94.4, 82.9, 70.6, 67.1, 38.8, 28.2; *m/z* (EI-MS) 453.1 $(M+Na)^+$.

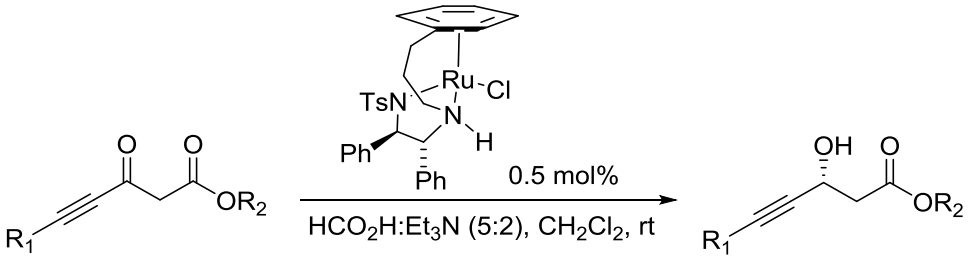
1,11-Dibenzyloxy-1,11-tetramethyl-2,9-nonadiyne-4,8-dione 200. This compound is novel.



This compound was prepared following the general procedure above using Weinreb diamide (327 mg, 1.5 mmol), *n*-BuLi (3.0 cm^3, 4.8 mmol), alkyne (870 mg, 5.0 mmol), and the product was isolated as described above as a yellow oil (527 mg, 1.19 mmol, 79%). (found (ESI): M^+ + Na, 467.2193. $C_{29}H_{32}O_4$ requires M, 467.2198); ν_{max} 2982, 2937, 2211, 1674, 1236, 1156, 1047, 735, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.32-7.18 (10H, m, 2 × Ph), 4.54 (4H, s, 2 × CH_2O), 2.54 (4H, t, *J* 7.1, 2 × $COCH_2$), 1.90 (2H, p, *J* 7.1, CH_2), 1.52 (12H, s, 4 × CH_3); δ_C (100 MHz, $CDCl_3$) 186.4, 138.4, 128.4, 127.6, 93.9, 83.2, 70.6, 67.0, 44.1, 28.3, 17.7; *m/z* (EI-MS) 467.1 $(M+Na)^+$.

3.13. Asymmetric Transfer Hydrogenation of Propargylic β-Keto Esters.

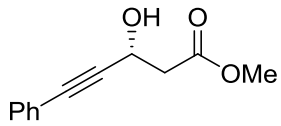
General Procedure



(*R*,*R*)-**c2** (0.6 mg, 1.0 × 10^{-3} mmol) and HCO_2H/Et_3N 5:2 azeotropic mixture (168 mg) was added into a flask and freshly prepared β-keto ester (0.2 mmol) in degassed CH_2Cl_2 (1 cm^3) was injected under a nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed (24-48 h). After quenched by sat $NaHCO_3$ (5 cm^3) the mixture was extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined organic extraction was

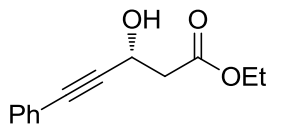
dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=10:1-5:1) to give the title products.

(3*R*)-Hydroxy-5-phenyl-4-pentynoic acid, methyl ester ***R*****-167.** This compound has been reported but not fully characterized.[182]



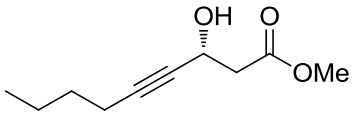
This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.6 mg, 1.0×10^{-3} mmol), ketone **143** (40.4 mg, 0.2 mmol), HCO_2H/Et_3N 5:2 (168 mg), CH_2Cl_2 (1.0 cm^3) and the product was isolated as a colourless oil (35.2 mg, 0.16 mmol, 86%, 96% ee). $[\alpha]_D^{31}$ +32.9 (c 0.8 in $CHCl_3$) 96 % ee (*R*); (found (ESI): M^+ + Na, 227.0679. $C_{12}H_{12}O_3$ requires M, 227.0684); ν_{max} 3445, 2954, 1724, 1163, 11040, 756, 690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.44-7.40 (2H, m, Ph), 7.33-7.27 (3H, m, Ph), 5.01 (1H, t, *J* 5.9, C*H*OH), 3.75 (3H, s, $COOCH_3$), 3.23 (1H, br, OH), 2.86 (1H, d, *J* 5.9, HC*H*), 2.85 (1H, s, *H*CH); δ_C (100 MHz, $CDCl_3$) 171.7, 131.8, 128.6, 128.3, 122.2, 88.0, 85.1, 59.2, 52.1, 41.9; *m/z* (EI-MS) 227.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:5, 0.6 cm^3/min, T = 30 °C. Retention times: (major - *R*) 20.1 min, (minor - *S*) 23.4 min.

(3*R*)-Hydroxy-5-phenyl-4-pentynoic acid, ethyl ester ***R*****-171.** This compound has been reported but not fully characterized.[183]



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.6 mg, 1.0 × 10^{-3} mmol), ketone **144** (43.2 mg, 0.2 mmol), HCO_2H/Et_3N 5:2 (168 mg), CH_2Cl_2 (1.0 cm^3) and the product was isolated as a colourless oil (41.4 mg, 0.19 mmol, 95%, 92% ee). $[\alpha]_D^{26}$ +18.9 (c 0.6 in $CHCl_3$) 92% ee (*R*); (found (ESI): M^+ + Na, 241.0835. $C_{13}H_{14}O_3$ requires M, 241.0840); ν_{max} 3429, 2982, 1717, 1159, 1025, 756, 690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.44-7.40 (2H, m, Ph), 7.35-7.27 (3H, m, Ph), 5.00 (1H, t, *J* 6.0, C*H*OH), 4.23 (2H, q, *J* 7.1, $COOCH_2$), 3.24 (1H, br, OH), 2.84 (2H, d, *J* 6.0, CH_2), 1.29 (3H, t, *J* 7.1, CH_3); δ_C (100 MHz, $CDCl_3$) 171.3, 131.8, 128.6, 128.3, 122.3, 88.3, 85.0, 61.1, 59.2, 42.2, 14.2; *m/z* (EI-MS) 241.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:5, 0.6 cm^3/min, T = 30 °C. Retention times: (major - *R*) 17.0 min, (minor - *S*) 20.6 min.

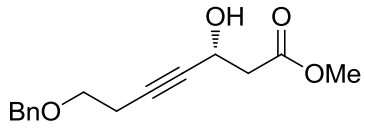
(3*R*)-Hydroxy-4-nonynoic acid, methyl ester *R*-169. This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.6 mg, 1.0 × 10^{-3} mmol), ketone **161** (41.0 mg, 0.22 mmol), HCO_2H/Et_3N 5:2 (168 mg), CH_2Cl_2 (1.0 cm^3) and the product was isolated as a colourless oil (38.0 mg, 20.6 mmol, 92%, 97% ee). $[\alpha]_D^{26}$ +27.1 (c 0.9 in $CHCl_3$) 97% ee (*R*); (found (ESI): M^+ + Na, 207.0992. $C_{10}H_{16}O_3$ requires M, 207.0997); ν_{max} 3475, 2958, 1738, 1438, 1276, 1162, 1022 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.71-4.65 (1H, m, C*H*OH), 3.66 (3H, s,$COOCH_3$), 3.00 (1H, d, *J* 5.7, OH), 2.66 (1H, d, *J* 1.6, *H*CHCOO), 2.65 (1H, s, HC*H*COO), 2.13 (2H, td, *J* 7.1, 2.0, $CH_2C\equiv$), 1.45-1.26 (4H, m, CH_2, CH_2), 0.83 (3H, t, *J* 7.2, CH_3); δ_C (100 MHz, $CDCl_3$) 171.8, 86.0, 79.3, 58.9, 51.9, 42.3, 30.5, 21.8, 18.3, 13.5; *m/z* (EI-MS) 207.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm),

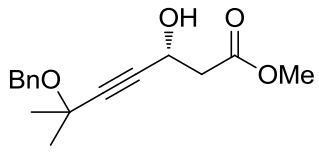
hexane:*i*-PrOH 96:4, 0.5 cm^3/min, T = 30 °C. Retention times: (major - *R*) 17.8 min, (minor - *S*) 17.0 min.

(3*R*)-Hydroxy-7-benzyloxy-4-heptynoic acid, methyl ester *R*-170. This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.6 mg, 1.0×10^{-3} mmol), ketone **162** (52.0 mg, 0.20 mmol), HCO_2H/Et_3N 5:2 (168 mg), CH_2Cl_2 (1.0 cm^3) and the product was isolated as a colourless oil (48.3 mg, 0.18 mmol, 92%, 97% ee). $[\alpha]_D^{28}$ +17.6 (c 1.0 in $CHCl_3$) 97 % ee (*R*); (found (ESI): M^+ + Na, 285.1097. $C_{15}H_{18}O_4$ requires M, 285.1102); ν_{max} 3427, 2865, 1735, 1163, 1096, 1062, 1027, 737, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.26 (5H, m, Ph), 4.78-4.72 (1H, m, C*H*OH), 4.54 (2H, s, PhCH_2), 3.72 (3H, s,$COOCH_3$), 3.57 (2H, t, *J* 7.0, BnOCH_2), 2.94 (1H, d, *J* 5.9, OH), 2.72 (2H, d, *J* 6.0, CH_2COO), 2.52 (2H, td, *J* 7.0, 1.9, $CH_2C\equiv$); δ_C (100 MHz, $CDCl_3$) 171.7, 138.0, 128.4, 127.8, 127.7, 82.5, 80.5, 72.9, 68.2, 58.8, 51.9, 42.2, 20.1; *m/z* (EI-MS) 285.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:4, 0.5 cm^3/min, T = 30 °C. Retention times: (major - *R*) 55.3 min, (minor - *S*) 53.0 min.

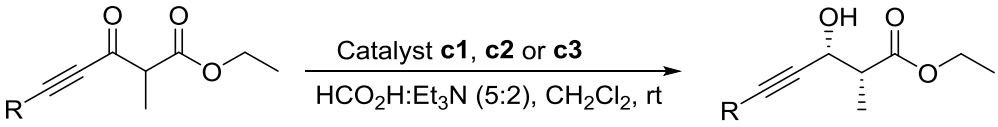
(3*R*)-Hydroxy-6-benzyloxy-6-methyl-4-heptynoic acid, methyl ester *R*-168. This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.6 mg, 1.0×10^{-3} mmol), ketone **160** (53.2 mg, 0.20 mmol), HCO_2H/Et_3N 5:2 (168 mg), CH_2Cl_2 (1.0 cm^3) and the product was isolated as a colourless oil (53.1 mg, 1.92 mmol, 99%, 99% ee). $[\alpha]_D^{28}$ +21.4 (c 0.8 in $CHCl_3$) 99 % ee (*R*); (found (ESI): M^+ + Na, 299.1254. $C_{16}H_{20}O_4$ requires M, 299.1259); ν_{max} 3420, 2983, 1736, 1154, 1049, 735, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35-7.15 (5H, m, Ph), 4.67-4.80 (1H, m, C*H*OH), 4.52 (2H, s, PhC*H*$_2$), 3.61 (3H, s, $COOCH_3$), 3.08 (1H, br, OH), 2.65 (2H, d, *J* 6.4, CH_2COO), 1.45 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 171.6, 139.0, 128.3, 127.7, 127.4, 87.4, 83.5, 70.5, 66.5, 58.8, 52.0, 42.0, 28.8; *m/z* (EI-MS) 299.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:4, 0.5 cm^3/min, T = 30 °C. Retention times: (major - *R*) 18.7 min, (minor - *S*) 18.1 min.

3.14. Asymmetric Transfer Hydrogenation Dynamic Kinetic Resolution of α-Methyl-β-keto Esters.

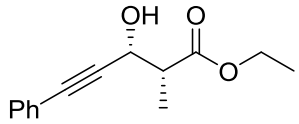
General Procedure



(*R*,*R*)-**c1** (4.2 mg, 6.7×10^{-3} mmol) or (*R*,*R*)-**c2** (0.6 mg, 1.0×10^{-3} mmol) or catalyst **c3** (3.4 mg, 6.7×10^{-3} mmol), HCO_2H/Et_3N 5:2 azeotropic mixture was added into a flask and freshly prepared β-keto ester (0.2 mmol) in degassed CH_2Cl_2 was injected under a nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed (48 h). After being quenched by sat $NaHCO_3$ (5 cm^3) the mixture was extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined organic extract was dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the crude product was purified by

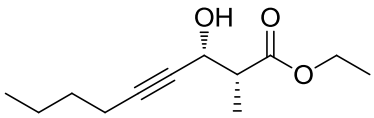
silica gel column chromatography (eluent hexane/EtOAc=10:1-5:1) to give the title products.

(2*R*)-Methyl-(3*R*)-hydroxy-5-phenyl-4-pentynoic acid, ethyl ester 172. This compound is novel.



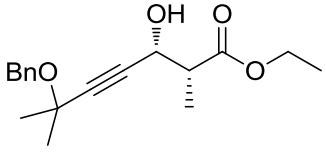
This compound was prepared following the general procedure above using (*R*,*R*)-**c1** catalyst (1.7 mg, 2.7 × 10^{-3} mmol), ketone **163** (20.0 mg, 0.087 mmol), HCO_2H/Et_3N 5:2 (84 mg), CH_2Cl_2 (0.5 cm^3) and the product was isolated as a colourless oil (20.0 mg, 0.086 mmol, 99%, 98% ee, dr 24/1).$[\alpha]_D^{23}$ +2.1 (c 0.3 in $CHCl_3$) 98% ee (2*R*,3*R*), dr 24/1; (found (ESI): M^+ + Na, 255.0992. $C_{14}H_{16}O_3$ requires M, 255.0997); ν_{max} 3450, 2982, 1717, 1188, 1027, 755, 690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.45-7.40 (2H, m, Ph), 7.34-7.27 (3H, m, Ph), 4.83 (1H, dd, *J* 6.9 4.1, C*H*OH), 4.22 (2H, q, *J* 6.7, $COOCH_2$), 3.15 (1H, d, *J* 6.9, OH), 2.88-2.81 (1H, m, CH), 1.37 (3H, d, *J* 7.2, CH_3), 1.29 (3H, t, *J* 6.7, $COOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 174.2, 131.8, 128.6, 128.3, 122.4, 87.3, 85.7, 64.3 61.0, 45.5, 14.2, 12.0; *m/z* (EI-MS) 255.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:4, 0.5 cm^3/min, T = 30 °C. Retention times: (major - 2*R*, 3*R*) 17.7 min, (minor - 2*S*, 3*S*) 25.2 min. 94% yield, 13/1 dr, >99% ee were obtained when (*R*,*R*)-**c2** (S/C=100/1) was used. 98% yield, 14/1 dr, >99% ee were obtained when (*S*,*S*)-**c2** (S/C=200/1) was used. 88% yield, 11/1 dr, were obtained when catalyst **c3** (S/C=30/1) was used.

(2*R*)-Methyl-(3*R*)-hydroxy-4-nonynoic acid, ethyl ester 173. This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c1** catalyst (4.2 mg, 6.7 × 10^{-3} mmol), ketone **165** (41.0 mg, 0.20 mmol), HCO_2H/Et_3N 5:2 (168 mg), CH_2Cl_2 (1.0 cm^3) and the product was isolated as a colourless oil (35.9 mg, 0.17 mmol, 87%, 99% ee, dr 27/1). $[\alpha]_D^{28}$ +4.7 (c 1.0 in $CHCl_3$) 99% ee (2*R*,3*R*), dr 27/1; (found (ESI): M^+ + Na, 235.1305. $C_{12}H_{20}O_3$ requires M, 235.1310); ν_{max} 3442, 2958, 2934, 2874, 1732, 1251, 1184, 1025 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.61-4.57(1H, m, C*H*OH), 4.19 (2H, q, *J* 7.1, $COOCH_2$), 3.04 (1H, d, *J* 7.1, OH), 2.71 (1H, td, *J* 7.2 4.2, C*H*CH_3), 2.20 (2H, td, *J* 6.9 2.0, $\equiv CCH_2$), 1.52-1.35 (4H, m, CH_2, CH_2), 1.29 (3H, t, *J* 7.1, $COOCH_2CH_3$), 1.28 (3H, d, *J* 7.2, $CHCH_3$), 0.90 (3H, t, *J* 7.2, $CH_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 174.3, 86.4, 78.5, 62.9, 60.8, 45.7, 30.6, 21.8, 18.3, 14.2, 13.5, 11.9; *m/z* (EI-MS) 235.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:4, 0.5 cm^3/min, T = 30 °C. Retention times: (major - 2*R*, 3*R*) 23.8 min, (minor - 2*S*, 3*S*) 21.4 min. 92% yield, 14/1 dr, >99% ee were obtained when (*R*,*R*)-**c2** (S/C=200/1) was used; 21% yield, 13/1 dr, were obtained when catalyst **c3** (S/C=30/1) was used.

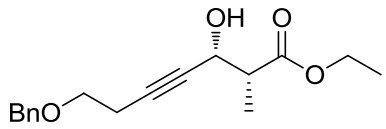
(2*R*)-Methyl-(3*R*)-hydroxy-6-benzyloxy-6-methyl-4-heptynoic acid, ethyl ester 174. This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c1** catalyst (4.2 mg, 6.7 × 10^{-3} mmol), ketone **164 (**60.4 mg, 0.20 mmol), HCO_2H/Et_3N 5:2 (168 mg), CH_2Cl_2 (1.0 cm^3) and the product was isolated as a colourless oil (54.9 mg, 0.18

mmol, 90%, 99% ee, dr 27/1). $[\alpha]_D^{28}$ +5.4 (c 0.6 in $CHCl_3$) 99% ee (2*R*,3*R*), dr 27/1; (found (ESI): M^+ + Na, 327.1567. $C_{18}H_{24}O_4$ requires M, 327.1572); ν_{max} 3441, 2983, 1732, 1244, 1186, 1156, 1041, 1028, 735, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.22 (5H, m, Ph), 4.62 (1H, dd, *J* 7.1 4.3, C*H*OH), 4.60 (2H, s, PhC*H*$_2$O), 4.16 (2H, q, *J* 7.1, COOC*H*$_2$), 3.12 (1H, d, *J* 7.1, OH), 2.78-2.71 (1H, m, C*H*CH_3), 1.53 (6H, s, 2 × CH_3), 1.30-1.24 (6H, m, CHC*H*$_3$ and COOCH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 174.0, 139.0, 128.3, 127.7, 127.4, 87.9, 82.8, 70.6, 66.6, 63.8, 61.0, 45.5, 28.9, 14.2, 12.1; *m/z* (EI-MS) 327.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:4, 0.5 cm^3/min, T = 30 °C. Retention times: (major - 2*R*, 3*R*) 16.6 min, (minor - 2*S*, 3*S*) 18.5 min. 97% yield, 12/1 dr, >99% ee were obtained when (*R*,*R*)-**c2** (S/C=200/1) was used.

(2*R*)-Methyl-(3*R*)-hydroxy-7-benzyloxy-4-heptynoic acid, ethyl ester 175. This compound is novel.

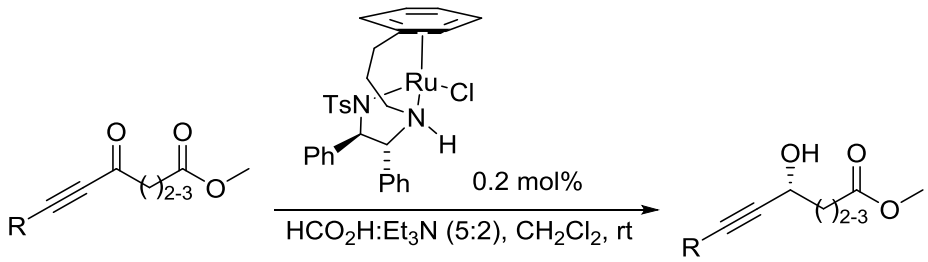


This compound was prepared following the general procedure above using (*R*,*R*)-**c1** catalyst (4.2 mg, 6.7 × 10^{-3} mmol), ketone **166** (61.2 mg, 0.21 mmol), HCO_2H/Et_3N 5:2 (168 mg), CH_2Cl_2 (1.0 cm^3) and the product was isolated as a colourless oil (46.5 mg, 0.16 mmol, 76%, >98% ee, dr 31/1). $[\alpha]_D^{28}$ +4.0 (c 0.7 in $CHCl_3$) 98% ee (2*R*,3*R*), dr 31/1; (found (ESI): M^+ + Na, 313.1410. $C_{17}H_{22}O_4$ requires M, 313.1415); ν_{max} 3446, 2981, 2939, 1729, 1187, 1094, 1027, 736, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.26 (5H, m, Ph), 4.62-4.58 (1H, m, C*H*OH), 4.53 (2H, s, PhC*H*$_2$O), 4.17 (2H, q, *J* 7.1, COOC*H*$_2$), 3.57 (2H, t, *J* 7.1, BnOC*H*$_2$), 3.02 (1H, d, *J* 6.9, OH), 2.70 (1H, qd, *J* 7.2 4.2, C*H*CH_3), 2.52 (2H, td, *J* 7.2 2.0, CH_2C≡), 1.28 (3H, d, *J* 7.2, CHC*H*$_3$), 1.26 (3H, t, *J* 7.1, COOCH$_2$C*H*$_3$); δ_C (100

MHz, $CDCl_3$) 174.3, 138.0, 128.4, 127.71, 127.70, 83.1, 79.6, 73.0, 68.3, 63.9, 60.9, 45.4, 20.1, 14.2, 11.8; *m/z* (EI-MS) 313.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:4, 0.8 cm^3/min, T = 30 °C. Retention times: (major - 2*R*, 3*R*) 39.9 min, (minor - 2*S*, 3*S*) 57.0 min. 92% yield, 14/1 dr, >99% ee were obtained when (*R*,*R*)-**c2** (S/C=200/1) was used.

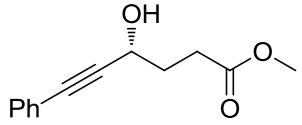
3.15. Asymmetric Transfer Hydrogenation of Propargylic γ and δ-Keto Esters.

General Procedure



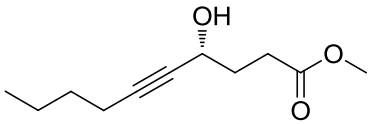
(*R*,*R*)-**c2** (0.6 mg, 1.0×10^{-3} mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture and γ or δ-keto esters (0.5 mmol) in degassed CH_2Cl_2 was injected under nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed (less than 72 h). After completion, the reaction was quenched by sat $NaHCO_3$ (10 cm^3) the mixture was extracted with CH_2Cl_2 (3 × 20 cm^3) and the combined organic extraction was dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=10:1-5:1) to give the products.

(4*R*)-Hydroxy-6-phenyl-5-hexynoic acid, methyl ester *R*-**184.** This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.6 mg, 1.0 × 10^{-3}mmol), 4-oxo-6-phenyl-5-hexynoic acid methyl ester **176** (118.0 mg, 5.5 mmol), HCO_2H/Et_3N 5:2 (105 mg) and CH_2Cl_2 (2.5 cm^3), and the product was isolated as a colourless oil (106.5 mg, 4.9 mmol, 89%, 94% ee). $[\alpha]_D^{24}$+13.3 (c 0.7 in $CHCl_3$) 94% ee (*R*); (found (ESI): M^+ + Na, 241.0835. $C_{13}H_{14}O_3$ requires M 241.0841); ν_{max} 3414, 2952, 1733, 1490, 1440, 1254, 1200, 1166, 1067, 756, 691 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.50-7.27 (5H, m, Ph), 4.71 (1H, t, *J* 6.0, C*H*OH), 3.69 (3H, s, $COOCH_3$), 2.70-2.54 (3H, m, CH_2COO, CHO*H*), 2.19-2.10 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 174.1, 131.7, 128.5, 128.3, 122.4, 89.1, 85.4, 62.0, 51.8, 32.5, 29.8; *m/z* (EI-MS) 241.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:5, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *R*) 18.6 min, (minor - *S*) 49.1 min.

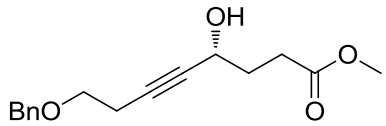
(4*R*)-Hydroxy-5-decynoic acid, methyl ester *R*-185. This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.6 mg, 1.0 × 10^{-3} mmol), ketone **177** (101 mg, 0.52 mmol), HCO_2H/Et_3N 5:2 (210 mg), CH_2Cl_2 (2.5 cm^3) and the product was isolated as a colourless oil (90.8 mg, 0.46 mmol, 89%, 93% ee). (found (ESI): M^+ + Na, 221.1148. $C_{11}H_{18}O_3$ requires M 221.1153); ν_{max} 3435, 2957, 2934, 1737, 1437, 1167, 1061 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.50-7.27 (5H, m, Ph), 4.38 (1H, br, C*H*OH), 3.61 (3H, s, $COOCH_3$), 2.64 (1H, br, CHO*H*), 2.53-2.39 (2H, m, CH_2COO), 2.13 (2H, t, *J* 6.9, $\equiv CCH_2$), 1.98-1.90 (2H, m, CH_2CH_2COO), 1.44-1.28 (4H, m, CH_2, CH_2), 0.84 (3H, t, *J* 7.2, CH_3); δ_C (100 MHz, $CDCl_3$) 174.2, 85.9, 80.3, 61.5, 51.7, 32.8, 30.6, 29.8, 21.9, 18.3, 13.5; *m/z* (EI-MS) 221.1 $(M+Na)^+$.HPLC separation

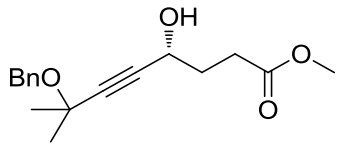
conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 94:6, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *R*) 50.8 min, (minor - *S*) 28.5 min.

(4*R*)-Hydroxy-8-benzyloxy-5-octynoic acid, methyl ester *R*-**187.** This compound is novel.



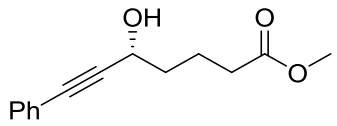
This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.4 mg, 6.7 × 10^{-4} mmol), ketone **179** (92.2 mg, 0.335 mmol), HCO_2H/Et_3N 5:2 (278 mg), CH_2Cl_2 (1.5 cm^3) and the product was isolated as a colourless oil (87.9 mg, 0.318 mmol, 95%, 98% ee). $[\alpha]_D^{34}$+ 8.3 (c 0.7 in $CHCl_3$) 98% ee (*R*); (found (ESI): M^+ + Na, 299.1254. $C_{16}H_{20}O_4$ requires M 299.1259); ν_{max} 3415, 2951, 2864, 1733, 1096, 1063, 737, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35-7.26 (5H, m, Ph), 4.54 (2H, s, PhC*H*$_2$O), 4.43 (1H, tt, *J* 6.1 2.0, C*H*OH), 3.67 (3H, s, $COOCH_3$), 3.57 (2H, t, *J* 7.0, BnOC*H*$_2$), 2.59-2.45 (5H, m, CH_2COO, $CH_2C\equiv$, OH), 1.99 (2H, td, *J* 7.2 7.1, C*H*$_2$ CH_2COO); δ_C (100 MHz, $CDCl_3$) 174.1, 138.0, 128.4, 127.8, 127.7, 82.7, 81.5, 73.0, 68.3, 61.6, 51.8, 32.7, 29.8, 20.1; *m/z* (EI-MS) 299.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:5, 0.7 cm^3/min, T = 30 °C. Retention times: (major - *R*) 26.4 min, (minor - *S*) 27.9 min.

(4*R*)-Hydroxy-7-benzyloxy-7-methyl-5-octynoic acid, methyl ester *R*-**186.** This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.4 mg, 6.7×10^{-4} mmol), ketone **178** (104 mg, 0.36 mmol), HCO_2H/Et_3N 5:2 (277 mg), CH_2Cl_2 (1.6 cm^3) and the product was isolated as a colourless oil (80.2 mg, 0.28 mmol, 77%, 99% ee). $[\alpha]_D^{28}$ +5.4 (c 1.2 in $CHCl_3$) 99% ee (*R*); (found (ESI): M^+ + Na, 313.1410. $C_{17}H_{22}O_4$ requires M 313.1415); ν_{max} 3424, 2987, 2935, 1736, 1244, 1154, 1052, 1027, 736, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.37-4.23 (5H, m, Ph), 4.60 (2H, s, PhC*H*$_2$O), 4.49 (1H, t, *J* 6.1, C*H*OH), 3.67 (3H, s, $COOCH_3$), 2.56-2.44 (2H, m, CH_2COO), 2.44 (1H, br, CHO*H*), 2.03-1.98 (2H, m, CH_2), 1.53 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 174.0, 139.0, 128.3, 127.6, 127.4, 87.6, 84.3, 70.6, 66.5, 61.4, 51.8, 32.5, 29.8, 29.0; *m/z* (EI-MS) 313.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 94:6, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *R*) 20.4 min, (minor - *S*) 19.2 min.

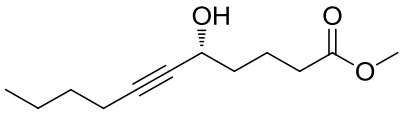
(5R)-Hydroxy-7-phenyl-6-heptynoic acid, methyl ester ***R*****-188.** This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.6 mg, 1.0×10^{-3} mmol), 5-oxo-7-phenyl-6-heptynoic acid methyl ester **180** (115 mg, 5.0 mmol), HCO_2H/Et_3N 5:2 (105 mg), CH_2Cl_2 (2.5 cm^3) and the product was isolated as a colourless oil (104 mg, 0.45 mmol, 89%, 96% ee). $[\alpha]_D^{24}$ + 0.5 (c 0.7 in $CHCl_3$) 96% ee (*R*); (found (ESI): M^+ + Na, 255.0992. $C_{14}H_{16}O_3$ requires M 255.0997); ν_{max} 3407, 2952, 1733, 1097, 1053, 756, 691 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36-7.34 (2H, m, Ph), 7.26-7.19 (3H, m, Ph), 4.54 (1H, t, *J* 6.0, C*H*OH), 3.60 (3H, s, $COOCH_3$), 2.35-2.32 (2H, m, CH_2COO), 2.26 (1H, br, CHO*H*), 1.85-1.73 (4H, m, CH_2CH_2); δ_C (100 MHz, $CDCl_3$) 174.0, 131.7, 128.4, 128.3, 122.5, 89.8, 85.1, 62.4, 51.6, 37.1, 33.6, 20.6. *m/z* (EI-MS)

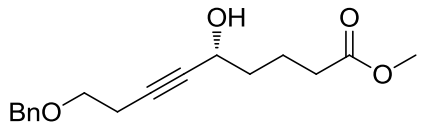
255.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:5, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *R*) 16.4 min, (minor - *S*) 68.5 min.

(5*R*)-Hydroxy-6-undecynoic acid, methyl ester *R*-189. This compound is novel.



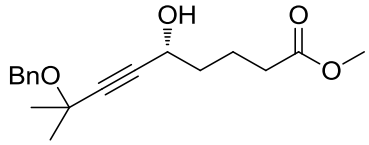
This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.6 mg, 1.0×10^{-3} mmol), ketone **181** (105 mg, mmol), HCO_2H/Et_3N 5:2 (415 mg), CH_2Cl_2 (2.0 cm^3) and the product was isolated as colourless oil (85.6 mg, 4.0 mmol, 81%, 99% ee). $[\alpha]_D^{34}$ + 4.1 (c 1.1 in $CHCl_3$) 99% ee (*R*); (found (ESI): M^+ + Na, 235.1305. $C_{12}H_{20}O_3$ requires M 235.1310); ν_{max} 3441, 2955, 2933, 1732, 1236, 1196, 1161, 1028 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.37 (1H, tt, *J* 6.4 1.9, C*H*OH), 3.68 (3H, s, $COOCH_3$), 2.55 (1H, br, OH), 2.37 (2H, t, *J* 7.5, CH_2COO), 2.20 (2H, td, *J* 6.9 1.9, $CH_2C\equiv$), 1.84-1.75 (2H, m, C*H*$_2CH_2COO$), 1.75-1.67 (2H, m, CH_2), 1.53-1.44 (2H, m, C*H*$_2CH_2CH_3$), 1.44-1.35 (2H, m, $CH_2CH_2CH_3$), 0.91 (3H, t, *J* 7.2, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 174.0, 85.7, 80.8, 62.1, 52.5, 37.4, 33.6, 30.7, 21.9, 20.6, 18.3, 13.6. *m/z* (EI-MS) 235.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IA column (250 mm × 4.6 mm), hexane:*i*-PrOH 100:0, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *R*) 13.35 min, (minor - *S*) 13.02 min. (chiral and racemic standard were analyzed by HPLC after conversion to the TBDPS ether)

(5*R*)-Hydroxy-9-benzyloxy-6-nonynoic acid, methyl ester *R*-191. This compound is novel.



This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.4 mg, 6.7 × 10^{-4} mmol), ketone **183** (101.2 mg, 3.51 mmol), HCO_2H/Et_3N 5:2 (277 mg), CH_2Cl_2 (1.6 cm^3) and the product was isolated as a colourless oil (101.1 mg, 3.48 mmol, 99%, 99% ee). $[\alpha]_D^{30}$ +5.5 (c 1.4 in $CHCl_3$) 99% ee (*R*); (found (ESI): M^+ + Na, 313.1410. $C_{17}H_{22}O_4$ requires M 313.1415); ν_{max} 3431, 2950, 2866, 1733, 1096, 1078, 1027, 737, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.25 (5H, m, Ph), 4.54 (2H, s, PhC*H*$_2$O), 4.37-4.31 (1H, m, C*H*OH), 3.66 (3H, s, $COOCH_3$), 3.57 (2H, t, *J* 7.0, BnOC*H*$_2$), 2.55 (1H, br, OH), 2.51 (2H, td, *J* 7.0, 2.0, $CH_2C\equiv$), 2.35 (2H, t, *J* 7.1, CH_2COO), 1.83-1.73 (2H, m, C*H*$_2$CHOH), 1.73-1.64 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 174.0, 138.0, 128.4, 127.8, 127.7, 82.2, 82.1, 72.9, 68.3, 62.0, 51.6, 37.2, 33.6, 20.6, 20.1. *m/z* (EI-MS) 313.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 94:6, 1.0 cm^3/min, T = 30 °C. Retention times: (major - *R*) 67.7 min, (minor - *S*) 66.2 min

(5*R*)-Hydroxy-8-benzyloxy-8-methyl-6-nonynoic acid, methyl ester ***R*-190.** This compound is novel.

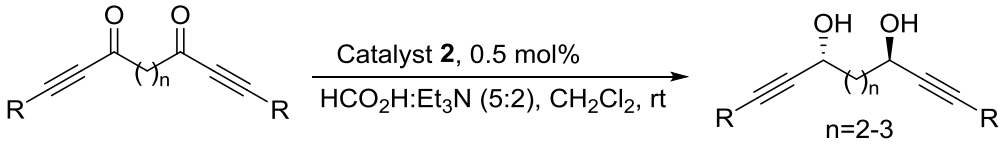


This compound was prepared following the general procedure above using (*R*,*R*)-**c2** (0.4 mg, 6.7 × 10^{-4} mmol), ketone **182** (101.0 mg, 0.334 mmol), HCO_2H/Et_3N 5:2 (280 mg), CH_2Cl_2 (1.6 cm^3) and the product was isolated as a colourless oil (85.7 mg, 0.28 mmol, 84%, 98% ee). $[\alpha]_D^{28}$ +10.1 (c 1.2 in $CHCl_3$) 98% ee (*R*); (found (ESI): M^+ + Na, 327.1567. $C_{18}H_{24}O_4$ requires M 327.1572); ν_{max} 3432, 2984, 1736, 1153, 1051, 1028, 736,

697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.22 (5H, m, Ph), 4.61 (2H, s, PhC*H*$_2$O), 4.39 (1H, t, *J* 6.2, CHOH), 3.65 (3H, s, $COOCH_3$), 2.35 (2H, t, *J* 7.2, CH_2COO), 2.24 (1H, br, CHO*H)*, 1.83-1.74 (2H, m, C*H*$_2$$CH_2COO$), 1.74-1.65 (2H, m, CH_2), 1.53 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 173.9, 139.1, 128.3, 127.6, 127.4, 87.2, 85.1, 70.6, 66.5, 61.9, 51.6, 37.1, 33.5, 29.0, 20.6. *m/z* (EI-MS) 327.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 94:6, 1.0 cm^3/min, T = 30 °C. Retention times: (major - *R*) 15.8 min, (minor - *S*) 19.1 min.

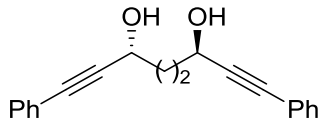
3.16. Asymmetric Transfer Hydrogenation of Propargylic 1,4-Diketones and 1,5-Diketones.

General Procedure



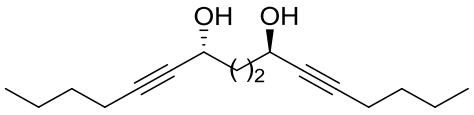
(*R*,*R*)-**c2** or (*S*,*S*)-**c2** (0.6 mg, 1.0 × 10^{-3} mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture (372 mg) and diketones (0.2 mmol) in degassed CH_2Cl_2 (2.0 cm^3) was injected under nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed (48 h). After the reaction was complete, sat $NaHCO_3$ (4 cm^3) and water (4 cm^3) was added and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were concentrated and dried over anhydrous $MgSO_4$ and purified by silica gel column chromatography (eluent hexane/EtOAc=6:1-3:1) to give the title products. In paper: The position of the *meso* compound in the chiral HPLC was established in each case by reducing a sample of ketone with a racemic sample of catalyst **c1** under the general conditions above.

1,8-Diphenyl-1,7-octadiyne-(3*R*, 6*R*)-diol (*R*,*R*)-**202.** This compound is known but not fully characterized.[184]



This compound was prepared following the general procedure above using both (*R*,*R*)-**c2** and (*S*,*S*)-**c2** (0.6 mg, 1.0×10^{-3} mmol), HCO_2H/Et_3N 5:2 azeotropic mixture (84 mg), diketone **197** (57.2 mg, 0.2 mmol) and degassed CH_2Cl_2 (1 cm^3). The product was isolated as described above as white crystals (47.1 mg, 0.16 mmol, 81%, >99% ee, de 93% for *R*,*R*-diol), (45.0 mg, 0.15 mmol, 78%, >99% ee, de 96% for *S*,*S*-diol). $[\alpha]_D^{28}$ +9.2 (c 0.9 in $CHCl_3$ for *R*,*R*-diol); $[\alpha]_D^{28}$ -8.5 (c 0.7 in $CHCl_3$ for *S*,*S*-diol); MP 76 °C; (found (ESI): M^+ + Na, 313.1199. $C_{20}H_{18}O_2$ requires M, 313.1204); ν_{max} 3191, 1488, 1004, 750, 687 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.44-7.42 (4H, m, 2 × Ph), 7.37-7.26 (6H, m, 2 × Ph), 4.74 (2H, t, *J* 5.7, 2 × C*H*OH), 2.81 (2H, s, 2 × OH), 2.16-2.01 (4H, m, 2 × CH_2); δ_C (100 MHz, $CDCl_3$) 185.1, 133.1, 130.9, 128.7, 119.8, 91.7, 87.5, 34.0; *m/z* (EI-MS) 313.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane: *i*-PrOH 80:20, 0.8 cm^3/min, T = 30 °C. Retention times, (*R*,*R*) 9.3 min, (*meso*) 24.8 min, (*S*,*S*) 51.2 min.

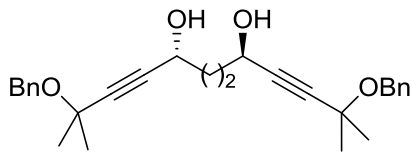
1,8-Dibutyl-1,7-octadiyne-(3*R*, 6*R*)-diol (*R*,*R*)-**203.** This compound is novel.



This compound was prepared following the general procedure above using both (*R*,*R*)-**c2** and (*S*,*S*)-**c2** (0.6 mg, 1.0×10^{-3} mmol), HCO_2H/Et_3N 5:2 azeotropic mixture (186 mg), diketone **201** (54.5 mg, 0.2 mmol) and degassed CH_2Cl_2 (2.0 cm^3). The product was isolated as described above as a colourless oil (48.1 mg, 0.19 mmol, 87%, >99% ee, de 95%

for *R*,*R*-diol), (45 mg, 0.18 mmol, 82%, >99% ee, de 93% for *S*,*S*-diol). $[\alpha]_D^{30}$ +14.9 (c 0.8 in $CHCl_3$ for *R*,*R*-diol); $[\alpha]_D^{30}$ -14.6 (c 0.7 in $CHCl_3$ for *S*,*S*-diol); (found (ESI): M^+ + Na, 273.1825. $C_{16}H_{26}O_2$ requires M, 273.1830); ν_{max} 3329, 2957, 2931, 2862, 1456, 1328, 1022 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.45 (2H, br, 2 × C*H*OH), 2.38-2.32 (2H, br, 2 × OH), 2.20 (4H, td, *J* 6.8 1.8, 2 × $CH_2C\equiv$), 1.94-1.82 (4H, m, 2 × CH_2CHOH), 1.52-1.45 (4H, m, 2 × C$H_2CH_2C\equiv$), 1.45-1.36 (4H, m, 2 × CH_2CH_3), 0.91 (6H, t, *J* 7.2, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 85.9, 80.8, 62.3, 33.7, 30.7, 21.9, 18.4, 13.6; *m/z* (EI-MS) 272.9 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 90:10,0.6 cm^3/min, T = 30 °C. Retention times, (*R*,*R*) 10.7 min, (*meso*) 12.5 min, (*S*,*S*) 11.1 min.

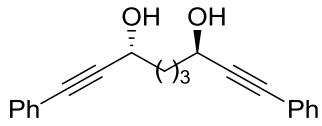
1,10-Dibenzyloxy-1,10-tetramethyl-2,8-octadiyne-(4*R*,7*R*)-diol (*R*,*R*)-**204.** This compound is novel.



This compound was prepared following the general procedure above using both (*R*,*R*)-**c2** and (*S*,*S*)-**c2** (0.3 mg, 5.0×10^{-4} mmol), HCO_2H/Et_3N 5:2 azeotropic mixture (186 mg), diketone **199** (41 mg, 0.1 mmol) and degassed CH_2Cl_2 (1.0 cm^3). The product was isolated as described above as a colourless oil (34.5 mg, 0.079 mmol, 83%, >99% ee, de 96% for *R*,*R*-diol), (29.1 mg, 0.067 mmol, 70%, >99% ee, de 98% for *S*,*S*-diol). $[\alpha]_D^{26}$ +13.5 (c 1.3 in $CHCl_3$ for *R*,*R*-diol); $[\alpha]_D^{30}$ -13.0 (c 1.5 in $CHCl_3$ for *S*,*S*-diol); (found (ESI): M^+ + Na, 457.2349. $C_{28}H_{34}O_4$ requires M, 457.2354); ν_{max} 3395, 2983, 1244, 1152, 1048, 1027, 734, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.22 (10H, m, 2 × Ph), 4.60 (4H, s, 2 × CH_2O), 4.45 (2H, br, 2 × C*H*OH), 2.62 (2H, s, 2 × OH), 1.96-1.77 (4H, m, 2 × CH_2), 1.52 (12H, s, 4 ×

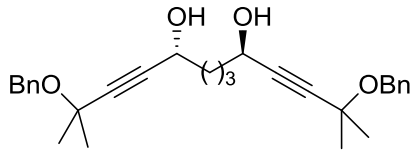
CH_3); δ_C (100 MHz, $CDCl_3$) 139.0, 128.4, 127.7, 127.4, 87.4, 84.9, 70.7, 66.5, 61.8, 33.3, 29.0; *m/z* (EI-MS) 457.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane: *i*-PrOH 95:5, 0.6 cm^3/min, T = 30 °C. Retention times, (*R*,*R*) 17.7 min, (*meso*) 21.0 min, (*S*,*S*) 19.6 min.

1,8-Nonadiyne-1,9-diphenyl-(3*R*,7*R*)-diol (*R*,*R*)-**205.** This compound is known but not fully characterized.[138]



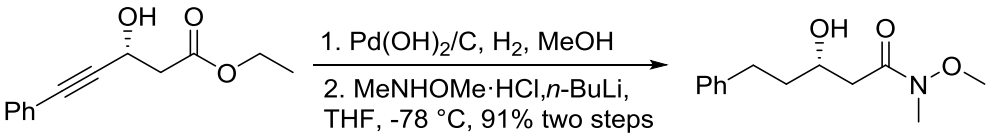
This compound was prepared following the general procedure above using both (*R*,*R*)-**c2** and (*S*,*S*)-**c2** (0.2 mg, 3.3×10^{-4} mmol), HCO_2H/Et_3N 5:2 azeotropic mixture (56 mg), diketone **198** (19.9 mg, 0.067 mmol) and degassed CH_2Cl_2 (0.5 cm^3).The product was isolated as described above as white crystals (19.4 mg, 0.064 mmol, 96%, >99% ee, 97% de for *R*,*R*-diol), (16.3 mg, 0.054 mmol, 81%, >99% ee, 97% de for *S*,*S*-diol). $[\alpha]_D^{23}$-26.2 (c 0.4 in $CHCl_3$) >99% ee (*S*,*S*), 97% de; $[\alpha]_D^{23}$ +30.9(c 0.2 in $CHCl_3$) >99% ee (*R*,*R*), 97% de; MP 102 °C; (found (ESI): M^+ + Na, 327.1356. $C_{21}H_{20}O_2$ requires M, 327.1361); ν_{max} 3348, 2949, 2915, 1489, 1416, 1107, 1068, 914, 758, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.43-7.37 (4H, m, 2 × Ph), 7.32-7.23 (6H, m, 2 × Ph), 4.64 (2H, t, *J* 6.4, 2 × C*H*OH), 2.24 (2H, s, 2 × OH), 1.93-1.84 (4H, m, 2 × CH_2), 1.83-1.74 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 131.7, 128.4, 128.3, 122.6, 89.9, 85.1, 62.8, 37.4, 21.1; *m/z* (EI-MS) 327.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane: *i*-PrOH 80:20, 0.8 cm^3/min, T = 30 °C. Retention times, (*R*,*R*) 9.9 min, (*meso*) 31.1 min, (*S*,*S*) 47.2 min.

1,11-Dibenzyloxy-1,11-tetramethyl-2,9-octadiyne-(4*R*, 8*R*)-diol (*R*,*R*)-**206.** This compound is novel.

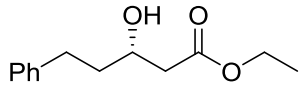


This compound was prepared following the general procedure above using both (*R*,*R*)-**c2** and (*S*,*S*)-**c2** (0.3 mg, 5.0×10^{-4} mmol), HCO_2H/Et_3N 5:2 azeotropic mixture (186 mg), diketone **200** (45.0 mg, 0.1 mmol) and degassed CH_2Cl_2 (1.0 cm^3). The product was isolated as described above as a colourless oil (38.9 mg, 0.8 mmol, 86%, >99% ee, de 97% for *R*,*R*-diol), (43.6 mg, 0.1 mmol, 97%, >99% ee, de >98% for *S*,*S*-diol). $[\alpha]_D^{28}$ + 0.29 (c 0.9 in $CHCl_3$ for *R*,*R*-diol); $[\alpha]_D^{28}$-0.23 (c 0.6 in $CHCl_3$ for *S*,*S*-diol); (found (ESI): M^+ + Na, 471.2506. $C_{29}H_{36}O_4$ requires M, 471.2511); ν_{max} 3380, 2984, 2934, 1243, 1152, 1049, 1027, 734, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.22 (10H, m, 2 × Ph), 4.60 (4H, s, 2 × CH_2O), 4.37 (2H, t, *J* 6.1, 2 × C*H*OH), 1.86 (2H, s, 2 × OH), 1.78-1.66 (4H, m, 2 × CH_2), 1.66-1.58 (2H, m, CH_2), 1.53 (12H, s, 4 × CH_3); δ_C (100 MHz, $CDCl_3$) 139.1, 128.3, 127.6, 127.4, 87.2, 85.3, 70.6, 66.5, 62.2, 37.4, 29.0, 21.0; *m/z* (EI-MS) 471.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IB column (250 mm × 4.6 mm), hexane: *i*-PrOH 95:5, 0.5 cm^3/min, T = 30 °C. Retention times, (*R*,*R*) 28.6 min, (*meso*) 31.8 min, (*S*,*S*) 33.2 min.

3.17. Total Synthesis of (-)-Yashabushidiol B.

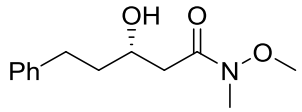


Ethyl (3*S*)-hydroxy-5-phenylpentanoate. This compound is known and has been fully characterized.[185]



Alcohol *R*-**171** (306 mg, 1.40 mmol, 92% ee) was stirred vigorously with $Pd(OH)_2/C$ (129 mg, 20% $Pd(OH)_2$) under 1 atm H_2 atmosphere at rt in degassed MeOH (10 cm^3). After 1h the catalyst was removed by filtration and washed with more MeOH. The eluent was concentrated and the product was used without purification. δ_H (400 MHz, $CDCl_3$) 7.31-7.24 (2H, m, Ph), 7.22-7.15 (3H, m, Ph), 4.16 (2H, s, *J* 7.2, $COOCH_2$), 4.06-3.98 (1H, m, C*H*OH), 2.86-2.78 (1H, d, *J* 2.8, PhHC*H*), 2.74-2.66 (1H, s, Ph*H*CH), 2.51 (1H, dd, *J* 12.4, 3.4, HC*H*COO), 2.44 (1H, dd, *J* 12.4, 8.6, *H*CHCOO), 1.90-1.69 (2H, m, CH_2CHOH), 1.27 (3H, t, *J* 7.2,CH_3); δ_C (100 MHz, $CDCl_3$) 173.0, 141.7, 128.5, 128.4, 125.9, 76.2, 60.8, 41.3, 38.1, 31.8, 14.2.

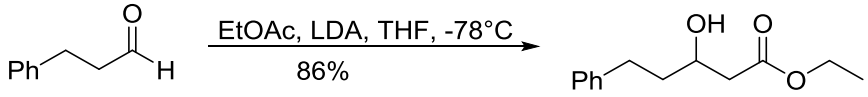
(3*S*)-Hydroxy-N-methoxy-N-methyl-benzenepentanamide 210. This compound is known and has been fully characterized.[186]



To a solution of *N*,*O*-dimethylhydroxylaminehydro chloride (549 mg, 5.6 mmol) in THF (8cm^3) *n*-BuLi (1.6 M in hexane, 6.9 cm^3, 11.0 mmol) was added dropwise at -78 °C. After stirring at room temperature for 10 min, the mixture was cooled to -78 °C, and a solution of the crude ethyl (3*S*)-hydroxy-5-phenylpentanoate (1.40 mmol) in THF (2.0 cm^3) was added. The reaction mixture was stirred at -78 °C for 4 h, then quenched with sat NH_4Cl (6 cm^3) and extracted with EtOAc (3× 20 cm^3). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=4:1-1:1) to afford the Weinreb amide **210** (288.1 mg, 1.28 mmol, 90% over two steps). $[\alpha]_D^{22}$+ 34.5 (c 0.5 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$)

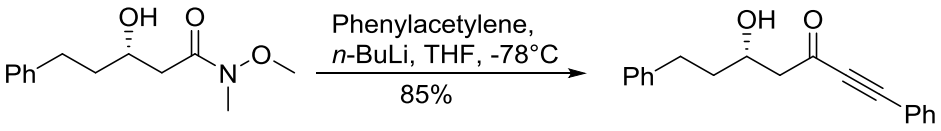
7.30-7.16 (5H, m, Ph), 4.08-4.01 (1H, m, C*H*OH), 3.88 (1H, d, *J* 2.9, OH), 3.67 (3H, s, OCH_3), 3.19 (3H, s, NCH_3), 2.86 (1H, ddd, *J* 13.8, 10.0, 5.4, *H*CHCON), 2.76-2.64 (2H, m, *H*CHCON and Ph*H*CH), 2.48 (1H, dd, *J* 16.8, 9.5, PhHC*H*), 1.94-1.84 (1H, m, *H*CHCHOH),1.78-1.70 (1H, m, HC*H*CHOH); δ_C (100 MHz, $CDCl_3$) 173.8, 142.0, 128.5, 128.4, 125.8, 67.2, 61.3, 38.2 (2C), 31.9 (2C); *m/z* (ESI-MS) 238.1 $(M+H)^+$. Lit[34] (*S*)-Weinreb amide $[\alpha]_D^{25}$ +28.6 (c=1.08, $CHCl_3$, >99% ee).

Ethyl hydroxy-5-phenylpentanoate. This compound is known and has been fully characterized. [185]



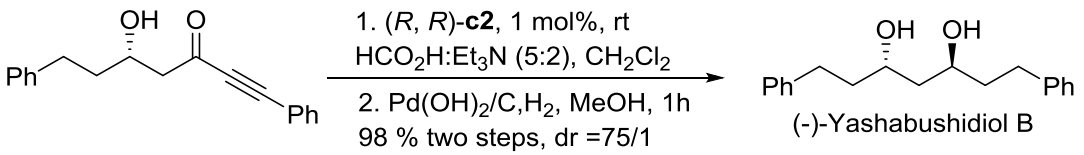
To a solution of diisopropylamine (3.23 g, 32 mmol) in THF (40 cm^3) at -78 °C was added *n*-BuLi (1.6 M in hexane, 20.0 cm^3, 32 mmol) dropwise over 20 min then a solution of ethylacetate (2.45 g, 27.8 mmol) in THF (10 cm^3) was added dropwise over 20 min. After stirring for 1.5 h, 3-phenylpropionaldehyde (3.16 g, 23.5 mmol in 10 cm^3 THF) was added in one portion. The resulting mixture was stirred at -78 °C for 2 h and sat NH_4Cl (50 cm^3) was added. The mixture was extracted with ethyl acetate (3 × 50 cm^3) and the combined organic phase was washed with brine (15 cm^3), and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=8:1) to afford the racemic compound as a colourless oil (4.5 g, 20.2 mmol, 86%). δ_H (400 MHz, $CDCl_3$) 7.31-7.24 (2H, m, Ph), 7.22-7.15 (3H, m, Ph), 4.16 (2H, s, *J* 7.2, $COOCH_2$), 4.06-3.98 (1H, m, C*H*OH), 2.86-2.78 (1H, d, *J* 2.8, PhHC*H*), 2.74-2.66 (1H, s, Ph*H*CH), 2.51 (1H, dd, *J* 12.4, 3.4, HC*H*COO), 2.44 (1H, dd, *J* 12.4, 8.6, *H*CHCOO), 1.90-1.69 (2H, m, CH_2CHOH), 1.27 (3H, t, *J* 7.2,CH_3).

(5*S*)-Hydroxy-1,7-diphenylhept-1-yn-3-one 212. This compound is known and has been fully characterized.[187]



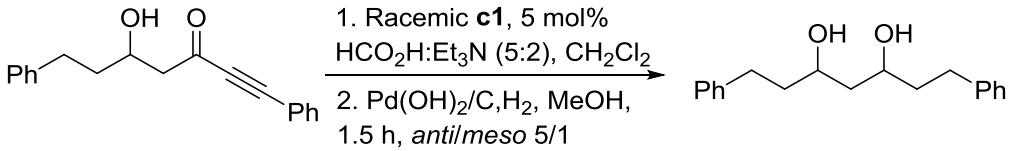
To a solution of phenylacetylene (146 mg, 1.45 mmol) in anhydrous THF (6 cm^3) at -78 °C, *n*-BuLi (1.6 M in hexane, 0.79 cm^3, 1.26 mmol) was added in 3 min. The mixture was stirred at -78 °C for 1 h and Weinreb amide **210** (81.1 mg in 0.5 cm^3 THF, 0.36 mmol) solution was added dropwise. After 30 min at -78 °C, temperature was raised to -10 °C for 2 h and sat NH_4Cl (5 cm^3) was added at -10 °C and the mixture was extracted with EtOAc (3 × 20 cm^3) and the combined organic phase was dried over anhydrous $MgSO_4$.The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc=8:1-5-1) to afford ketone **212** as a light yellow solid (86.0 mg, 0.30 mmol, 85%). MP 43-44 °C; $[\alpha]_D^{26}$ + 27.6 (c 0.5 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.60-7.54 (2H, m, Ph), 7.50-7.45 (1H, m, Ph), 7.42-7.37 (2H, m, Ph), 7.32-7.27 (2H, m, Ph), 7.24-7.17 (3H, m, Ph), 4.24-4.17 (1H, m, C*H*OH), 2.91-2.80 (3H, m, CH_2CO and OH), 2.77-2.69 (2H, m, C*H*$_2$Ph), 1.93-1.73 (2H, m, C*H*$_2$CH$_2$Ph); ^{13}C NMR (100 MHz, $CDCl_3$) 186.3, 140.6, 132.1, 130.0, 127.6, 127.4 (2C), 124.9, 118.6, 90.9, 86.8, 65.9, 51.3, 37.0, 30.7; *m/z* (ESI-MS) 279.1 $(M+H)^+$. Lit[187] MP 45-50 °C; *S* enantiomer $[\alpha]_D$ +17.7 (c 1.0 in $CHCl_3$, 96% ee).

(-)-Yashabushidiol B 213. This compound is known and has been fully characterized.[139-141]



(*R*,*R*)-**c2** (0.3 mg, 5×10^{-4} mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture (60 mg) and ketone **212** (13.2 mg, 0.047 mmol) in degassed CH_2Cl_2 (0.5 cm^3) was injected under nitrogen atmosphere. The mixture was stirred at rt until the starting material was completely consumed then the reaction was quenched by sat $NaHCO_3$ (0.5 cm^3), extracted with EtOAc (3 × 5 cm^3) and the combined organic phase was dried over anhydrous $MgSO_4$. After concentration, $Pd(OH)_2/C$ (5 mg, 20% $Pd(OH)_2$) and MeOH (2.0 cm^3) was added. The solution was degassed once and stirred vigorously under a1 atm H_2 atmosphere for 1 h. The catalyst was removed by filtration and washed by MeOH. The product solution were concentrated and purified by silica gel column chromatography (eluent hexane/EtOAc=6:1-2:1) to afford (-)-yashabushidiol B as white needles (13.2 mg, 0.047 mmol, 98%, >99 ee, dr > 20/1 (determined by ^1H NMR), dr = 75/1 (determined by HPLC)). MP 87 °C; $[\alpha]_D^{22}$ - 5.0(c 0.5 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.31-7.24 (4H, m, 2 × Ph), 7.22-7.16 (6H, m, 2 × Ph), 4.03-3.94 (2H, m, 2 × C*H*OH), 2.78 (2H, ddd, *J* 13.7 8.9 5.8, 2 × HC*H*Ph), 2.66 (2H, ddd, *J* 13.7 8.4 6.5, 2 × HC*H*Ph), 2.34 (2H, br, 2 × OH), 1.91-1.82 (2H, m, 2 × HC*H*CH_2Ph), 1.82-1.71 (2H, m, 2 × HC*H*CH_2Ph), 1.67 (2H, t, *J* 6.2, CHC*H*$_2$CH); δ_C (100 MHz, $CDCl_3$) 141.9, 128.5, 128.4, 125.9, 68.9, 42.6, 39.1, 32.2. *m/z* (ESI-MS) 285.1 $(M+H)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm x 4.6 mm), hexane: *i*-PrOH 92:8, 0.8 cm^3/min, T = 30 °C. Retention times, (*R*,*R*) 16.0 min, (*S*,*S*) 17.7 min, (*meso*) 21.6 min. Lit[140] MP 91-92 °C; ($[\alpha]_D$ -7.3 (c=1, $CHCl_3$).

Racemic+*meso* Yashabushidiol B.

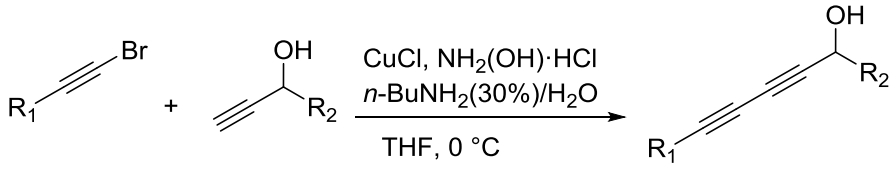


Racemic catalyst **c1** (6 mg, 0.01 mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture (84 mg) and ketone ±**212** (60 mg, 0.21 mmol) in degassed CH_2Cl_2 (1.5 cm^3) was injected under a nitrogen atmosphere. The mixture was stirred at rt until the starting material was completely consumed and the reaction was quenched by sat $NaHCO_3$ (1 cm^3), extracted with CH_2Cl_2 (3 × 5 cm^3) and the combined organic phase was dried over anhydrous $MgSO_4$. After concentration, $Pd(OH)_2/C$ (30 mg, 20% $Pd(OH)_2$) and MeOH (10 cm^3) was added. The solution was degassed once and stirred vigorously under 1 atm H_2 atmosphere for 1.5 h. The catalyst was removed by filtration and washed with MeOH. The solution was concentrated and purified by silica gel column chromatography (eluent hexane/EtOAc=6:1-2:1) to afforded yashabushidiol B as a white solid (dr 5/1). δ_H (400 MHz, $CDCl_3$) 7.31-7.24 (4H, m, 2 × Ph), 7.22-7.16 (6H, m, 2 × Ph), 4.03-3.94 (2H, m, 2 × C*H*OH), 2.78 (2H, ddd, *J* 13.7 8.9 5.8, 2 × HC*H*Ph), 2.66 (2H, ddd, *J* 13.7 8.4 6.5, 2 × HC*H*Ph), 2.34 (2H, br, 2 × OH), 1.91-1.82 (2H, m, 2 × HC*H*CH_2Ph), 1.82-1.71 (2H, m, 2 × HC*H*CH_2Ph), 1.67 (2H, t, *J* 6.2, CHCH_2CH). (racemic and *meso* diols were unable to be differentiated by ^{1}H NMR)

Racemic reduction catalyst **c1** was prepared by combining equal masses of each enantiomerically-pure catalyst. Due to weighing errors on the small scale required, the product exhibits a small residual enantiomeric excess (see HPLC in supporting information).

3.18. Synthesis of Racemic Diynols.

General Procedure



CuCl powder (6 mg, 2 mol%, 0.06 mmol) was added to a solution of degassed *n*-$BuNH_2$(30%)/H_2O (7.5 cm^3) at 0 °C. The blue colour was quenched by the addition of a spatula's tip of $NH_2OH{\cdot}HCl$. An alkyne solution (3.3 mmol, 1.1 equiv in THF 1 cm^3) was added and the reaction mixture was stirred for 5 min then bromoalkyne (3.0 mmol, 1.0 equiv in THF 1 cm^3) was added. Every few minutes a spatula's tip of $NH_2OH{\cdot}HCl$ (0.66 equiv in total) was added to the reaction mixture. After starting material was completely consumed (monitored by TLC 30 min to 2 h) the mixture was warmed to rt, quenched with sat NH_4Cl (10 cm^3) and extracted with CH_2Cl_2 (3 × 30 cm^3). The organic extracts were combined and dried with sodium sulfate, filtered, concentrated and purified by column chromatography (hexane:EtOAc ratios are dependent on the polarity of products) to afford pure products. Full characterisation data is given for the asymmetric products.

6-Phenyl-3,5-hexadiyne-2-ol 215. This compound is known but not fully characterized.[188]

This compound was prepared following the general procedure above using CuCl (20 mg, 0.2 mmol), $NH_2OH{\cdot}HCl$ (690 mg, 6.0 mmol), 3-butyn-2-ol (770 mg, 11.0 mmol), (bromoethynyl)benzene (1.82 g, 10.0 mmol) and *n*-$BuNH_2$(30%)/H_2O solution (26 cm^3). The product was isolated as a white solid (1.53 g, 9.0 mmol, 90%).

7-Benzyloxy-7-methyl-3,5-octadiyne-2-ol 216. This compound is novel.

This compound was prepared following the general procedure above using CuCl (11 mg, 0.11 mmol), $NH_2OH{\cdot}HCl$ (235 mg, 3.36 mmol), 4-bromo-3-butyn-2-ol (998 mg, 6.76 mmol), [[(1,1-dimethyl-2-propyn-1-yl)oxy]methyl]-benzene (978 mg, 5.6 mmol) and *n*-$BuNH_2$(30%)/H_2O solution (14.0 cm^3). The product was isolated as colourless oil (1.10 g, 4.5 mmol, 79%).

3,5-Decadiyne-2-ol 217. This compound is novel.

This compound was prepared following the general procedure above using CuCl (6.0 mg, 0.06 mmol), $NH_2OH{\cdot}HCl$ (126 mg, 1.8 mmol), 3-butyn-2-ol (234 mg, 3.3 mmol), 1-bromohex-1-yne (486 mg, 3.0 mmol) and *n*-$BuNH_2$(30%)/H_2O solution (7.5 cm^3).The product was isolated as colourless oil (309 mg, 2.1 mmol, 69%).

5,7-Dodecadiyne-4-ol 218. This compound is novel.

This compound was prepared following the general procedure above using CuCl (6.0 mg, 0.06 mmol), $NH_2OH{\cdot}HCl$ (126 mg, 1.8 mmol), 1-hexyn-3-ol (323 mg, 3.3 mmol), 1-bromohex-1-yne (485 mg, 3.0 mmol) and *n*-$BuNH_2$(30%)/H_2O solution (7.5 cm^3). The product was isolated as colourless oil (471 mg, 2.6 mmol, 88%).

5,7-Decadiyne-1,9-diol 219. This compound is known but not fully characterized.[189]

This compound was prepared following the general procedure above using CuCl (21 mg, 0.2 mmol), $NH_2OH{\cdot}HCl$ (421 mg, 6.06 mmol), 4-bromo-3-butyn-2-ol (1.80 g, 12.2 mmol), 5-hexyn-1-ol (996 mg, 10.1 mmol) and *n*-$BuNH_2$(30%)/H_2O solution (26 cm^3). The product was isolated as colourless oil (1.65 g, 9.9 mmol, 98%).

1-Phenyl-3,5-decadiyne-2-ol 220. This compound is novel.

This compound was prepared following the general procedure above using CuCl (6.0 mg, 0.06 mmol), $NH_2OH{\cdot}HCl$ (128 mg, 1.68 mmol), 1-phenylbut-3-yn-2-ol (438 mg, 3.0 mmol), 1-bromohex-1-yne (660 mg, 3.3 mmol) and *n*-$BuNH_2$(30%)/H_2O solution (7.0 cm^3). The product was isolated as colourless oil (488 mg, 2.2 mmol, 72%).

5-(1'-Benzyoxyl-cyclohexanyl)-3,5-hexadiyn-2-ol 221. This compound is novel.

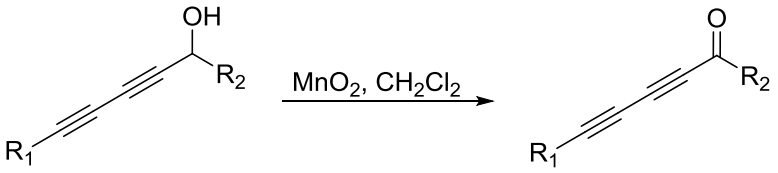
This compound was prepared following the general procedure above using CuCl (6.0 mg, 0.06 mmol), $NH_2OH{\cdot}HCl$ (117 mg, 1.68 mmol), 4-bromo-3-butyn-2-ol (488 mg, 3.3 mmol), [[(1-ethynylcyclohexyl)oxy]methyl]-benzene (642 mg, 3.0 mmol) and *n*-$BuNH_2$(30%)/H_2O solution (7.0 cm^3). The product was isolated as colourless oil (820 mg, 2.9 mmol, 97%).

2,8-Dimethyl-2-benzyloxy-3,5-nonadiyne-7-ol 222. This compound is novel.

This compound was prepared following the general procedure above using CuCl (6 mg, 0.06 mmol), $NH_2OH{\cdot}HCl$ (128 mg, 1.68 mmol), 1-bromo-4-methyl-1-pentyn-3-ol (532 mg, 3.0 mmol), [[(1,1-dimethyl-2-propyn-1-yl)oxy]methyl]-benzene (574 mg, 3.3 mmol) and *n*-$BuNH_2$(30%)/H_2O solution (7.0 cm^3). The product was isolated as colourless oil (589 mg, 2.2 mmol, 73%).

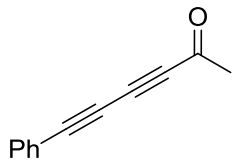
3.19. Synthesis of Diynones.

General Procedure



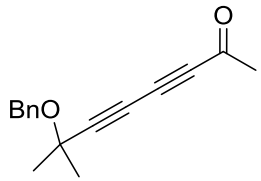
Alcohol (1.0 mmol) was dissolved in CH_2Cl_2 (8 cm^3) and activated MnO_2 power (2.0-2.3 g) was added. After stirringat rt for 30 min to 1 h; MnO_2 was filtered and washed with CH_2Cl_2. The filtratrate was concentrated and purified by silica gel column chromatography (pure CH_2Cl_2) to afford the pure products.

6-Phenyl-3,5-hexadiyn-2-one 223. This compound is known and has been fully characterized.[190]



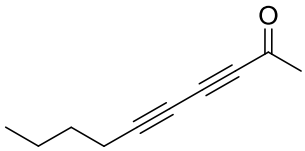
This compound was prepared following the general procedure above using alcohol **215** (22.5 mg, 0.132 mmol) and MnO_2 (150 mg, 1.7 mmol). The product was isolated as a yellow solid (21.7 mg, 0.129 mmol, 98%). ν_{max} 2207, 1657, 1185, 753, 682 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.57-7.52 (2H, m, Ph), 7.47-7.42 (1H, m, Ph), 7.39-7.34 (2H, m, Ph), 2.41(3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 183.4, 133.0, 130.5, 128.7, 120.2, 86.5, 78.6, 75.1, 72.1, 32.6.

7-Benzyloxy-7-methyl-3,5-octadiyn-2-one 224. This compound is novel.



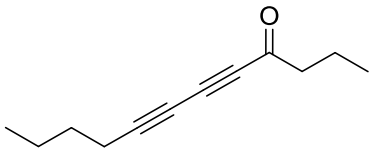
This compound was prepared following the general procedure above using alcohol **216** (242 mg, 1.0 mmol) and MnO_2 (2.3 g, 27 mmol). The product was isolated as a colourless oil (203 mg, 0.85 mmol, 85%). (found (ESI): M^+ + Na, 263.1043; $C_{16}H_{16}O_2$ requires M, 263.1042); ν_{max} 2987, 2231, 2139, 1674, 1202, 1183, 1155, 1048, 732, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.25 (5H, m, Ph), 4.61 (2H, s, C*H*$_2$Ph), 2.37 (3H, s, CH_3CO), 1.59 (6H, s, 2 × CH_3C); δ_C (100 MHz, $CDCl_3$) 182.3, 138.2, 128.4, 127.73, 127.69, 90.4, 75.8, 74.2, 71.2, 67.4, 67.2, 32.6, 28.3; *m/z* (ESI-MS) 263.1 $(M+Na)^+$.

3,5-Decadiyn-2-one 225. This compound is known and has been fully characterized.[191]



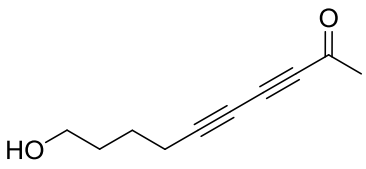
This compound was prepared following the general procedure above using alcohol **217** (179 mg, 1.2 mmol) and MnO_2 (2.7 g, 31 mmol). The product was isolated as a ketone/CH_2Cl_2 4/1 mixture and was used directly after purification. δ_H (400 MHz, $CDCl_3$) 2.38 (2H, t, *J* 7.0, $\equiv CCH_2$), 2.35 (3H, s, CH_3CO), 1.61-1.52 (2H, m, $\equiv CCH_2CH_2$), 1.48-1.38 (2H, m, CH_2CH_3), 0.93 (3H, t, *J* 7.3, CH_3).

5,7-Dodecadiyn-4-one 226. This compound is novel.



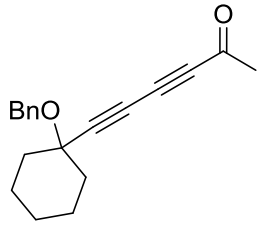
This compound was prepared following the general procedure above using alcohol **218** (178 mg, 1.0 mmol) and MnO_2 (2.0 g, 23 mmol). The product was isolated as a colourless oil (145 mg, 0.82 mmol, 82%). (found (ESI): $M^+ + H$, 177.1274; $C_{12}H_{16}O$ requires M, 177.1274); ν_{max} 2961, 2934, 2230, 2145, 1667, 1269, 1230 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.54 (2H, t, *J* 7.3, CH_2CO), 2.38 (2H, t, *J* 7.0, $\equiv CCH_2$), 1.75-1.65 (2H, m, $CH_3CH_2CH_2CO$), 1.60-1.52 (2H, m, $\equiv CCH_2CH_2$), 1.49-1.38 (2H, m, $\equiv CCH_2CH_2$ CH_2), 0.95 (3H, t, *J* 7.5, CH_3), 0.93 (3H, t,*J* 7.4, CH_3); δ_C (100 MHz, $CDCl_3$) 187.2, 90.6, 76.1, 72.2, 63.8, 47.3, 29.8, 21.9, 19.3, 17.5, 13.4 (2 C); *m/z* (ESI-MS) 199.1 $(M+Na)^+$.

1-Hydroxyl-5,7-decadiyn-9-one 227. This compound is novel.



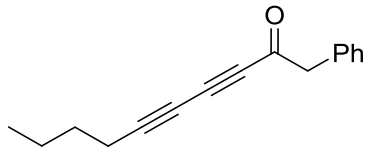
This compound was prepared following the general procedure above using alcohol **219** (168 mg, 1.0 mmol) and MnO_2 (2.3 g, 27 mmol). The product was isolated as a colourless oil (150 mg, 0.9 mmol, 90%). (found (ESI): M^+ + Na, 187.0730; $C_{10}H_{12}O_2$ requires M 187.0729); ν_{max} 3325, 2938, 2226, 2145, 1668, 1262, 1133, 619 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.72-3.64 (2H, m, C*H*$_2$OH), 2.40-2.47 (2H, m, ≡C*H*$_2$), 2.36 (2H, s, CH_3CO), 1.73-1.65 (4H, m, C*H*$_2$C*H*$_2$CH$_2$OH), 1.44 (1H, br, OH); δ_C (100 MHz, $CDCl_3$) 183.7, 90.5, 75.9, 72.7, 64.1, 62.1, 32.6, 31.6, 24.2, 19.5; *m/z* (ESI-MS) 187.1 $(M+Na)^+$.

5-(1'-Benzyoxyl-cyclohexanyl)-3,5-hexadiyn-2-one 229. This compound is novel.



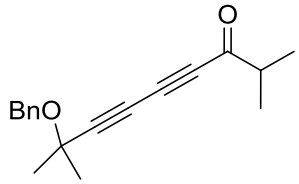
This compound was prepared following the general procedure above using alcohol **221** (282 mg, 1.0 mmol) and MnO_2 (2.3 g, 27 mmol). The product was isolated as a colourless oil (200 mg, 0.7 mmol, 71%). (found (ESI): M^+ + Na, 303.1356; $C_{19}H_{20}O_2$ requires M, 303.1356); ν_{max} 2935, 2868, 2228, 2137, 1673, 1237, 1132, 1087, 1067, 735, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.25 (5H, m, Ph), 4.62 (2H, s, C*H*$_2$Ph), 2.38 (2H, s, CH_3CO), 2.06-1.97 (2H, m, cycle hexanyl), 1.82-1.67 (4H, m, cycle hexanyl), 1.60-1.48 (3H, m, cycle hexanyl), 1.40-1.28 (1H, m, cycle hexanyl); δ_C (100 MHz, $CDCl_3$) 183.4, 138.5, 128.4, 127.7, 127.6, 90.3, 75.6, 74.4, 69.0, 66.1, 36.8, 32.6, 25.2, 22.6; *m/z* (ESI-MS) 303.1 $(M+Na)^+$.

1-Phenyl-3,5-decadiyn-2-one 228. This compound is novel.



This compound was prepared following the general procedure above using alcohol **220** (226 mg, 1.0 mmol) and MnO_2 (2.3 g, 27 mmol). The product was isolated as yellow oil (56 mg, 0.25 mmol, 25%). (found (ESI): $M^+ + H$, 225.1274; $C_{16}H_{16}O$ requires M, 225.1274); ν_{max} 2959, 2933, 2228, 2144, 1665, 1310, 701 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.21 (5H, m, Ph), 3.84 (2H, s, C*H*$_2$Ph), 2.35 (2H, t, *J* 7.0, ≡CCH_2), 1.59-1.49 (2H, m, ≡CCH_2C*H*$_2$), 1.46-1.36 (2H, m, C*H*$_2$$CH_3$), 0.91 (3H, t, *J* 7.3, CH_3); δ_C (100 MHz, $CDCl_3$) 184.1, 132.5, 129.8, 128.8, 127.5, 91.5, 77.9, 72.1, 63.8, 52.1, 29.7, 21.9, 19.4, 13.5; *m/z* (ESI-MS) 247.1 $(M+Na)^+$.

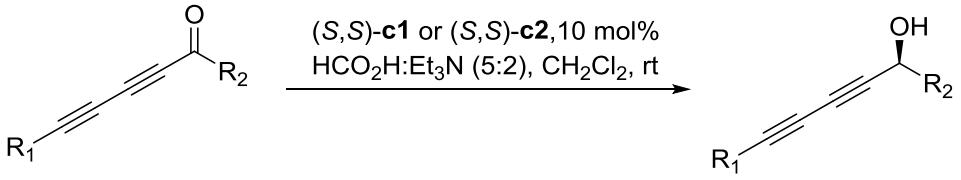
2,8-Dimethyl-2-benzyloxy-3,5-nonadiyn-7-one 230. This compound is novel.



This compound was prepared following the general procedure above using alcohol **222** (134 mg, 0.5 mmol) and MnO_2 (1.20 g, 14 mmol). The product was isolated as a colourless oil (131 mg, 0.5 mmol, 98%). (found (ESI): $M + H^+$, 269.1536; $C_{18}H_{20}O_2$ requires M, 269.1536); ν_{max} 3032, 2229, 2136, 1183, 1050, 1001, 733, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.26 (5H, m, Ph), 4.62 (2H, s, C*H*$_2$Ph), 2.73-2.62 (1H, m, CH), 1.59 (6H, s, 2 × CH_3C), 1.21 (6H, d, *J* 7.0, 2 × C*H*$_3$CH); δ_C (100 MHz, $CDCl_3$) 190.9, 138.3, 128.4, 127.7, 127.6, 89.9, 75.2, 74.8, 71.2, 67.6, 67.1, 43.1, 28.4, 17.7; *m/z* (ESI-MS) 291.1 $(M+Na)^+$.

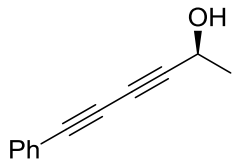
3.20. Asymmetric Transfer Hydrogenation of Diynones.

General Procedure



(S,*S*)-**c2**/(S,*S*)-**c1** (3.0 mg, 5.0×10^{-3} mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture (84 mg) and diynone (0.05 mmol) in degassed CH_2Cl_2 (0.5 cm^3) was injected. The mixture was stirred at rt until starting material was completely consumed (1-3 h). The reaction mixture was quenched by sat NH_4Cl (4 cm^3) and extracted with dichloromethane (3 × 10 cm^3). The combined organic phase was dried over anhydrous $MgSO_4$, concentrated and purified by silica gel column chromatography (eluent hexane/EtOAc).

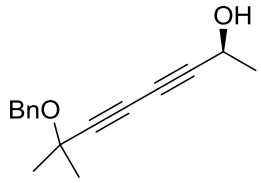
6-Phenyl-3,5-hexadiyn-(2*S*)-ol *S*-**215.** This compound is known but not fully characterized.[188]



This compound was prepared following the general procedure above using (*S*,*S*)-**c1** (3.0 mg, 5.0×10^{-3} mmol), HCO_2H/TEA 5:2 (83 mg) and ketone **223** (8.4 mg, 0.05 mmol). The product was isolated as a white solid (2.1 mg, 0.013 mmol, 25 %, 94 % ee). $[\alpha]_D^{24}$ -58.4 (c 0.1 in $CHCl_3$) 94% ee (*S*); MP 29 °C; ν_{max} 3312, 2982, 2236, 1126, 1067, 751, 684 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.50-7.47 (2H, m, Ph), 7.38-7.28 (3H, m, Ph), 4.66 (1H, q, *J* 6.6, CH), 2.17 (1H, br, OH), 1.52 (3H, d, *J* 6.6, CH_3); δ_C (00 MHz, $CDCl_3$) 132.6, 129.3, 128.4, 121.5, 84.0, 77.8, 73.2, 68.9, 58.9, 24.0; *m/z* (ESI-MS) 193.0 $(M+Na)^+$. HPLC

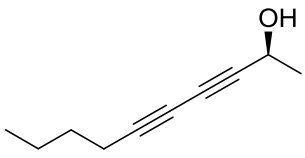
separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:05, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *S*) 13.4 min, (minor - *R*) 15.6 min.

7-Benzyloxy-7-methyl-3,5-octadiyne-(2*S*)-ol *S*-216. This compound is novel.



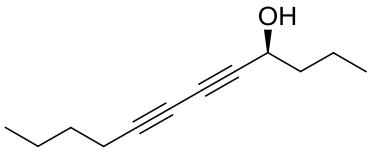
This compound was prepared following the general procedure above using both (*S*,*S*)-**c1** (3.0 mg, 5.0 × 10^{-3} mmol) and (*S*,*S*)-**c2** (3.0 mg, 5.0 × 10^{-3} mmol), HCO_2H/TEA 5:2 (83 mg) and ketone **224** (12.0 mg, 0.05 mmol). The product was isolated as a colourless oil (10.4 mg, 0.043 mmol, 86%, ee 94% for non-tethered catalyst) and (9.9 mg, 0.041 mmol, 82 %, ee 93% for tethered catalyst). $[\alpha]_D^{22}$ -30.5 (c 0.3 in $CHCl_3$) 93% ee (*S*);found (ESI): M^+ + Na, 265.1199; $C_{16}H_{18}O_2$ requires M, 265.1199); ν_{max} 3384, 2984, 1264, 1147, 1084, 1046, 1026, 735, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.25 (5H, m, Ph), 4.61 (2H, s, C*H*$_2$Ph), 4.61-4.52 (1H, m, CH), 2.05 (1H, br, OH), 1.55 (6H, s, 2 × CH_3C), 1.47 (3H, d, *J* 6.6, CH_3); δ_C (100 MHz, $CDCl_3$) 138.6, 128.4, 127.8, 127.5, 82.1, 81.0, 71.1, 68.4, 68.2, 66.9, 58.7, 28.7, 23.9; *m/z* (ESI-MS) 265.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:04, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *S*) 10.3 min, (minor - *R*) 10.8 min.

3,5-Decadiyne-(2*S*)-ol *S*-217. This compound is novel.



This compound was prepared following the general procedure above using (*S*,*S*)-**c1** (3.0 mg, 5.0×10^{-3} mmol) or (*S*,*S*)-**c2** (3.0 mg, 5.0×10^{-3} mmol), HCO_2H/TEA 5:2 (83 mg) and ketone **225** (7.4 mg, 0.05 mmol). The product was isolated as a colourless oil (7.0 mg, 0.047 mmol, 94 %, ee 97% for non-tethered catalyst) and (5.6 mg, 0.037 mmol, 75 %, ee 97% for tethered catalyst). $[\alpha]_D^{22}$ -20.6 (c 0.7 in $CHCl_3$) 97% ee (*S*); (found (ESI): M^+ + Na, 173.0937; $C_{10}H_{14}O$ requires M, 173.0937); ν_{max} 3329, 2959, 2933, 2257, 1097, 1074, 1027 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.57 (1H, m, CH), 2.28 (2H, t, *J* 6.9, $CH_2C\equiv$), 1.99 (1H, d, *J* 5.3, OH), 1.55-1.37 (4H, m, $CH_3CH_2CH_2$), 1.46 (3H, d, *J* 6.7, CH_3), 0.91 (3H, t, *J* 7.3, CH_3); δ_C (100 MHz, $CDCl_3$) 81.9, 77.1, 69.2, 64.3, 58.7, 30.2, 24.1, 21.9, 18.9, 13.5; *m/z* (ESI-MS) 173.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:04, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *S*) 10.6 min, (minor - *R*) 12.1 min.

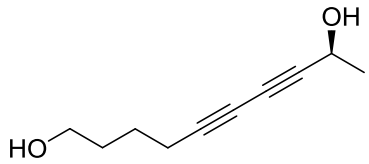
3,5-Decadiyne-(4*S*)-ol ***S*-218.** This compound is novel.



This compound was prepared following the general procedure above using (*S*,*S*)-**c1** (3.0 mg, 5.0×10^{-3} mmol) or (*S*,*S*)-**c2** (3.0 mg, 5.0×10^{-3} mmol), HCO_2H/TEA 5:2 (83 mg) and ketone **226** (8.8 mg, 0.05 mmol). The product was isolated as a colourless oil (8.1 mg, 0.046 mmol, 91%, ee 97% for non-tethered catalyst) and (8.4 mg, 0.047 mmol, 95%, ee 98% for tethered catalyst). $[\alpha]_D^{22}$ -0.3 (c 0.6 in $CHCl_3$) 98% ee (*S*); (found (ESI): M^+ + Na, 201.1250; $C_{12}H_{18}O$ requires M 201.1249); ν_{max} 3317, 2959, 2933, 2872, 2254, 1464, 1113 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.42 (1H, t, *J* 5.5, C*H*OH), 2.29 (2H, t, *J* 6.8, $CH_2C\equiv$), 1.91-1.62 (3H, m, CH_2CHOH), 1.57-1.36 (6H, m, CH_2CH_3 and $CH_2CH_2CH_3$), 0.99-.088 (6H,

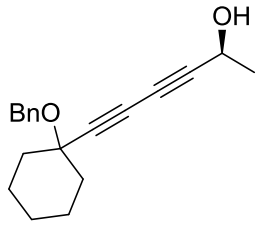
m, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 81.7, 76.5, 69.9, 64.4, 62.7, 39.7, 30.2, 21.9, 19.0, 18.4, 13.7, 13.5; *m/z* (ESI-MS) 201.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 97:03, 0.6 cm^3/min, T = 30 °C. Retention times: (major - *S*) 10.4 min, (minor - *R*) 11.2 min. (this compound was protected as the *p*-$MeOC_6H_4CO$ ester and used for HPLC)

5,7-Decadiyne-1,(9*S*)-diol ***S*-219.** This compound is known but not fully characterized.



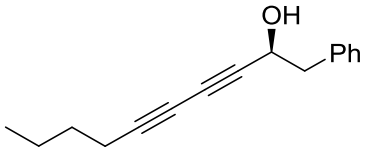
This compound was prepared following the general procedure above using (*S*,*S*)-**c1** (3.0 mg, 5.0×10^{-3} mmol) or (*S*,*S*)-**c2** (3.0 mg, 5.0×10^{-3} mmol), HCO_2H/TEA 5:2 (83 mg) and ketone **227** (8.3 mg, 0.05 mmol). The product was isolated as a colourless oil (7.5 mg, 0.045 mmol, 89 %, ee >90% for non-tethered catalyst) and (8.0 mg, 0.047 mmol, 96 %, ee >90% for tethered catalyst). $[\alpha]_D^{24}$ -8.6 (c 0.4 in $CHCl_3$) >90% ee (*S*); (found (ESI): M^+ + Na, 189.0886; $C_{10}H_{14}O_2$ requires M 189.0886); ν_{max} 3321, 2935, 2254, 1322, 1098, 1060, 1030 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.59-4.53 (1H, m, C*H*OH), 3.67 (2H, t, *J* 5.8, CH_2OH), 2.46 (1H, d, *J* 5.1, CHO*H*), 2.34 (2H, t, *J* 6.8, $CH_2C\equiv$), 1.76-1.59 (5H, m, CH_2CH_2CH_2O*H*), 1.46 (3H, d, *J* 6.6, CH_3); δ_C (100 MHz, $CDCl_3$) 81.3, 77.5, 69.0, 64.7, 66.2, 58.6, 31.7, 24.5, 24.1, 19.1; *m/z* (ESI-MS) 189.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 100:0, 0.6 cm^3/min, T = 30 °C. Retention times: (major - *S*) 11.8 min, (minor - *R*) 12.3 min. (this diol was protected by TBDPS and used for HPLC)

5-(1'-Benzyoxyl-cyclohexanyl)-3,5-hexadiyn-(2*S*)-ol ***S*-221.** This compound is novel.



This compound was prepared following the general procedure above using (*S*,*S*)-**c1**(3.1 mg, 5.0×10^{-3} mmol) or (*S*,*S*)-**c2** (3.0 mg, 5.0×10^{-3} mmol), HCO_2H/TEA 5:2 (83 mg) and ketone **229** (14.0 mg, 0.05 mmol). The product was isolated as a colourless oil (11.9 mg, 0.042 mmol, 85%, ee 95% for non-tethered catalyst) and (10.6 mg, 0.038 mmol, 76%, ee 90% for tethered catalyst). $[\alpha]_D^{22}$ +7.9 (c 0.4 in $CHCl_3$) 95% ee (*S*); (found (ESI): M^+ + Na, 305.1512; $C_{19}H_{22}O_2$ requires M, 305.1512); ν_{max} 3362, 2933, 2857, 1087, 1066, 934, 733, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.30 (4H, m, Ph), 7.23-7.29 (1H, m, Ph), 4.63 (2H, s, C*H*$_2$Ph), 4.59-4.52 (1H, m, CH), 2.19-2.15 (1H, br, OH), 2.03-1.93 (2H, m, cyclohexyl), 1.75-1.66 (4H, m, cyclohexyl), 1.61-1.47 (3H, m, cyclohexyl), 1.46 (3H, d, *J* 6.7, CH_3), 1.38-1.25 (1H, m, cyclohexyl); δ_C (100 MHz, $CDCl_3$) 138.3, 128.4, 127.8, 127.5, 81.7, 80.7, 74.7, 70.0, 68.4, 65.9, 58.7, 37.1, 25.3, 24.0, 22.7; *m/z* (ESI-MS) 305.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 97:3, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *S*) 13.0 min, (minor - *R*) 13.9 min.

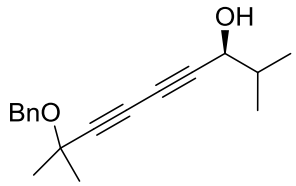
1-Phenyl-3,5-decadiyne-(2*S*)-ol *S*-**220.** This compound is novel.



This compound was prepared following the general procedure above using (*S*,*S*)-**c1** (3.0 mg, 5.0×10^{-3} mmol) or (*S*,*S*)-**c2** (3.0 mg, 5.0×10^{-3} mmol), HCO_2H/TEA 5:2 (83 mg) and ketone **228** (11.2 mg, 0.05 mmol). The product was isolated as a colourless oil (10.2 mg,

0.045 mmol, 90 %, ee 97% for non-tethered catalyst) and (10.5 mg, 0.046 mmol, 92 %, ee 98% for tethered catalyst). $[\alpha]_D^{22}$ -22.0 (c 0.8 in $CHCl_3$) 97% ee (*S*); (found (ESI): M^+ + Na, 249.1250; $C_{16}H_{18}O$ requires M, 249.1250); ν_{max} 3332, 2957, 2930, 2253, 1454, 1029, 747, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35-7.23 (5H, m, Ph), 4.61(1H, q, *J* 6.1, ≡CCH), 3.03 (1H, dd, *J* 13.4 6.1, HC*H*Ph), 2.98 (1H, dd, *J* 13.4 6.1, *H*CHPh), 2.28 (2H, t, *J* 7.4, ≡CCH_2), 1.93 (1H, d, *J* 6.1, OH), 1.55-1.47 (2H, m, ≡CCH_2CH_2), 1.46-1.36 (2H, m, CH_2 CH_3), 0.91 (3H, t, *J* 7.3, CH_3); δ_C (100 MHz, $CDCl_3$) 136.2, 129.8, 128.5, 127.0, 82.1, 75.6, 70.9, 64.3, 63.6, 43.9, 30.2, 21.9, 19.0, 13.5; *m/z* (ESI-MS) 249.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 97:3, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *S*) 15.9 min, (minor - *R*) 19.7 min.

2,8-Dimethyl-2-benzyloxy-3,5-nonadiyne-(7*S*)-ol *S*-**222.** This compound is novel.

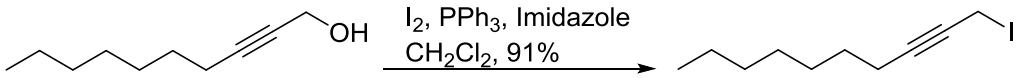


This compound was prepared following the general procedure above using (*S*,*S*)-**c1** (3.0 mg, 5.0×10^{-3} mmol) or (*S*,*S*)-**c2** (3.0 mg, 5.0×10^{-3} mmol), HCO_2H/TEA 5:2 (83 mg) and ketone **230** (13.3 mg, 0.05 mmol). The product was isolated as a colourless oil (10.6 mg, 0.039 mmol, 79 %, ee 96% for non-tethered catalyst) and (12.7 mg, 0.048 mmol, 95%, ee 99% for tethered catalyst). $[\alpha]_D^{24}$ +4.9 (c 0.5 in $CHCl_3$) 99% ee (*S*); (found (ESI): M^+ + Na, 293.1512; $C_{18}H_{22}O_2$ requires M, 293.1512); ν_{max} 3374, 2963, 2933, 1147, 1027, 735, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.24 (5H, m, Ph), 4.62 (2H, s, CH_2Ph), 4.23 (1H, t, *J* 5.7, C*H*OH), 1.98 (1H, br, OH,), 1.94-1.86 (1H, m, C*H*$(CH_3)_2$), 1.56 (6H, s, 2 × CH_3C), 1.02 (3H, d, *J* 6.8, CHCH_3), 1.01 (3H, d, *J* 6.8, CHCH_3); δ_C (100 MHz, $CDCl_3$) 138.6, 128.4, 127.8, 127.5, 81.6, 79.4, 71.1, 69.6, 68.6, 68.3, 66.9, 34.6, 28.7, 18.1, 17.5; *m/z* (ESI-MS)

293.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 97:3, 0.8 cm^3/min, T = 30 °C. Retention times: (major - *S*) 8.9 min, (minor - *R*) 10.7 min.

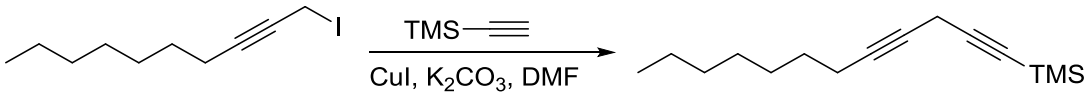
3.21. Total Synthesis of Panaxjapyne A.

1-Iodo-2-decyne 236. This compound is novel.



I_2 (1.448 g, 5.7 mmol) was added to a vigorouslystirred solution of imidazole (2.135 g, 6.4 mmol) and PPh_3 (1.573 g, 6.0 mmol) in dry CH_2Cl_2 (13 cm^3). The resulting solution was stirred for 10 min then a solution of 2-decyn-1-ol **231** (655 mg, 4.25 mmol) in dry CH_2Cl_2 (5 cm^3) was added via syringe. The mixture was stirred for 30 min and the solid residue was removed by filtration and rinsed with hexane (100 cm^3). The solution was concentrated and purified by column chromatography (pure hexane) to give the product **236** as a colourless oil (1.02 g, 3.9 mmol,91%). ν_{max} 2924, 2854, 1463, 1170, 1142, 557 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.71 (2H, t, *J* 2.4, CH_2I), 2.21-2.16 (2H, m, $\equiv CCH_2$), 1.53-1.46 (2H, m, $\equiv CCH_2CH_2$), 1.40-1.24 (8H, m, $CH_2CH_2CH_2CH_2CH_3$), 0.89 (3H, t, *J* 6.9, CH_3); δ_C (100 MHz, $CDCl_3$) 86.9, 77.0, 31.7, 29.1, 28.8, 28.4, 22.6, 19.1, 14.1, -16.6. No response was found from ether ESI-MS or HRMS.

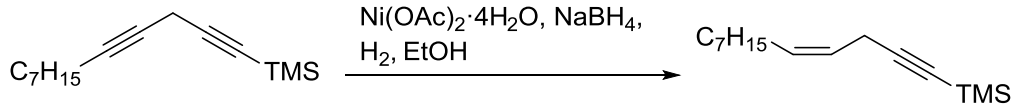
Trimethyl-1,4-dodecadiynylsilane 237. This compound is novel.



Ground K_2CO_3 power (370 mg, 2.7 mmol) and CuI (231 mg, 1.2 mmol) powder were dried at 140 °C undervacuum for 30 min. After cooled to rt, anhydrous DMF (9.5 cm^3) was injected followed by ethynyltrimethylsilane (1.33 cm^3, 9.5 mmol). The suspension

was stirred for 10 min then a solution of 1-iodo-2-decyne **236** (500 mg, 1.9 mmol) in DMF (3 cm^3) was added and stirring was continued for 24 h. Sat NH_4Cl (20 cm^3) and water (20 cm^3) were added and the mixture was extracted with hexane/Et_2O 4/1 mixture (2 × 40 cm^3), and the organic extracts were dried over anhydrous $MgSO_4$. After concentration the crude product was purified by column chromatography (pure hexane) to afford product **237** as yellow oil (329 mg, 1.4 mmol, 74 %). (found (ESI): M^+ + H, 235.1877. $C_{15}H_{26}Si$ requires M, 235.1876); ν_{max} 2957, 2928, 2856, 2183, 1249, 1012, 840 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.03 (2H, t, *J* 2.4, ≡CC*H*$_2$CH≡), 1.99 (2H, tt, *J* 7.0, 2.4, ≡CC*H*$_2$), 1.36-1.27 (2H, m, ≡CCH$_2$C*H*$_2$), 1.25-1.06 (8H, m, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.72 (3H, t, *J* 7.0, CH_3), -0.25 (9H, s, Si(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 100.9, 84.7, 81.2, 73.4, 31.8, 28.9, 28,8, 28.7, 22.7, 18.8, 14.1, 11.0, 0.03; *m/z* (ESI-MS) 257.1 $(M+Na)^+$.

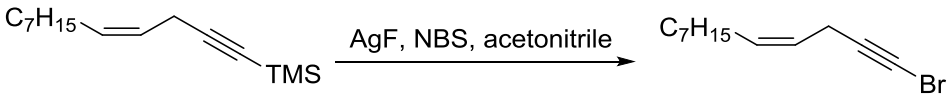
(4Z)-4-Dodecen-1-ynyltrimethylsilane 234. This compound is known but not fully characterized.[192]



$Ni(OAc)_2·4H_2O$ (46.0 mg, 0.185 mmol) was dissolved in EtOH (4.0 cm^3) and treated with a suspension of $NaBH_4$ (6.8 mg, 0.185 mmol) in EtOH (3.0 cm^3) under hydrogen. After stirringfor 15 min., ethylenediamine (27.8 mg, 0.46 mmol) in EtOH (2.0 cm^3) was added. After stirring for 1.5 h, a solution of freshly prepared diyne (213 mg, 0.91 mmol) in EtOH (2.0 cm^3) was added and the mixture was stirred vigorously for 55 min (longer reaction time cause yield decrease). The EtOH was removed and the residue was purified by column chromatography (pure hexane) to afford product **234** as acolourless oil (190 mg, 0.81 mmol, 88%, Z/E 23/1). (found (ESI): M^+ + Na, 259.1852. $C_{15}H_{28}Si$ requires M, 259.1852); ν_{max} 2957, 2924, 2855, 2176, 1249, 839, 759 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.36-

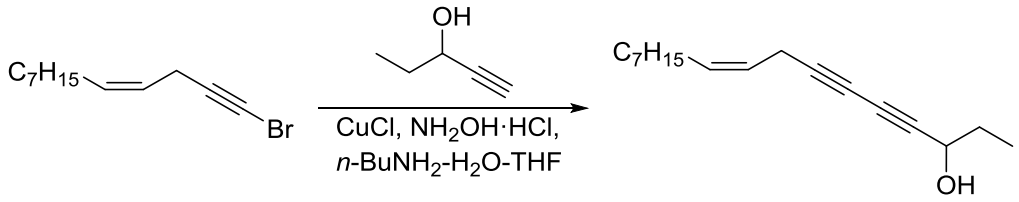
5.23 (2H, m, CH=CH), 2.83 (2H, d, *J* 6.0, ≡CC*H*$_2$CH=), 1.88 (2H, q, *J* 6.8, =CHC*H*$_2$), 1.26-1.07 (10H, m, (C*H*$_2$)$_5$CH$_3$), 0.74 (3H, t, *J* 7.0, CH$_3$), -0.25 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, CDCl$_3$) 131.9, 123.6, 105.4, 83.9, 31.7, 29.2, 29.11, 29.08, 27.1, 22.5, 18.3, 14.0, 0.0; *m/z* (ESI-MS) 473.4 $(2M+H)^+$.

1-Bromo-(4*Z*)-dodecen-1-yne 238. This compound is novel.



To a solution of **234** (77 mg, 0.33 mmol) in acetonitrile (3.5 cm^3) was added NBS (70 mg, 0.39 mmol) and AgF (49.5 mg, 0.39 mmol). After the reaction had completed (30 min), the mixture was diluted with water (10 cm^3), extracted with hexane (3 × 20 cm^3) and dried over anhydrous MgSO$_4$. After concentration, the crude product was purified by a short column (pure hexane) to afford product **238** as colourless oil (73.3 mg,0.30 mmol, 93%). ν_{max} 2955, 2924, 2854, 1464, 723 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 5.54-5.45 (1H, m, C*H*=CH), 5.44-5.35 (1H, m, C*H*=CH), 2.95 (2H, d, *J* 6.8, ≡CCH$_2$CH=), 2.02 (2H, q, *J* 7.2, =CCH$_2$), 1.40-1.20 (10H, m, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.88 (3H, t, *J* 7.0, CH$_3$); δ_C (100 MHz, CDCl$_3$) 132.5, 122.9, 78.6, 37.8, 31.9, 29.3, 29.20, 29.18, 27.2, 22.7, 18.0, 14.1. No response was found from ether ESI-MS or HRMS.

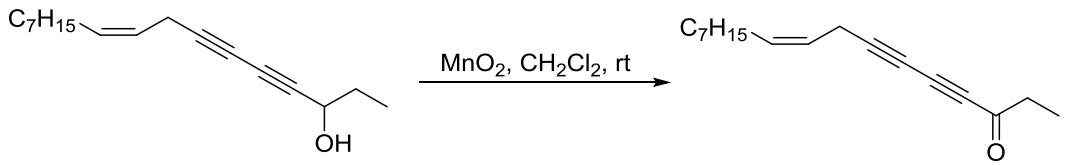
(±)-Panaxjapyne A ±239. This compound is known and has been fully characterized.



CuCl power (2.1 mg, 0.022 mmol, 3 mol%) was added to a solution of degassed *n*-BuNH$_2$(30%)/H$_2$O (1.6 cm^3) at 0 °C. The blue colour was quenched by the addition of a

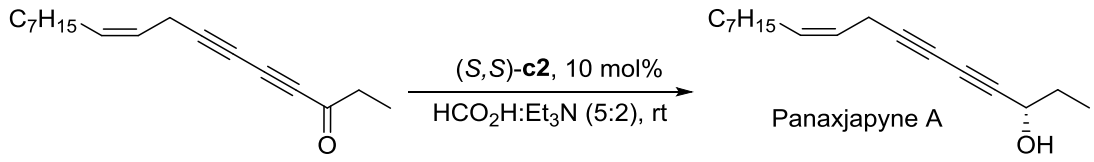
spatula's tip of $NH_2OH{\cdot}HCl$. 1-Pentyn-3-ol (89 mg, 1.05 mmol, 1.5 equiv in THF) was added and the reaction mixture was stirred for 1 min then freshly prepared 1-bromo-(4*Z*)-dodecen-1-yne (170 mg, 0.69 mmol in THF) was added. Every few minutes a spatula's tip of $NH_2OH{\cdot}HCl$ (31.3 mg, 0.45 mmol as total amount) was added to the mixture. After the starting material had been completely consumed (about 30 min, monitored by TLC) the mixture was quenched usingsat NH_4Cl (4 cm^3), warmed to rt and extracted with CH_2Cl_2 (3 × 20 cm^3). The organic extracts were dried over anhydrous $MgSO_4$, concentrated and purified by column chromatography (hexane:EtOAc 20/1-10/1) to afford (±)-panaxjapyne A as a colourless oil (155.1 mg, 0.63 mmol, 90%).

Panaxjapynone A. This compound is novel.

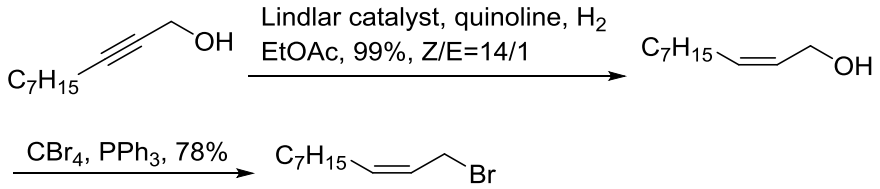


Alcohol ±**239** (154.5 mg, 0.63 mmol) in CH_2Cl_2 (4.5 cm^3) was treated with activated MnO_2 (2.0 g). After strirring at rt for 1.5 h, the MnO_2 was filtered and the solid residue was rinsed with CH_2Cl_2 (30 cm^3). The organic filterate was concentrated and purified by a short silica gel column (hexane:EtOAc 20/1) to afford pure panaxjapynone A as light yellow oil (112.2 mg, 0.46 mmol, 73%). (found (ESI): M^+ + H, 245.1900. $C_{17}H_{24}O$ requires M, 245.1900); ν_{max} 2920, 2855, 2233, 2145, 1673, 1235, 1101, 1037 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.60-5.52 (1H, m, C*H*=CH), 5.42-5.33 (1H, m, CH=C*H*), 3.11 (2H, d, *J* 6.9, ≡CC*H*$_2$CH=), 2.58 (2H, q, *J* 7.3, COC*H*$_2$), 2.03 (2H, q, *J* 7.3, =CHC*H*$_2$), 1.42-1.22 (10H, m, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.14 (3H, t, *J* 7.4, COCH$_2$C*H*$_3$), 0.88 (3H, t, *J* 7.1, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 187.6, 133.9, 120.8, 88.2, 76.0, 72.4, 63.5, 38.8, 31.8, 29.2 (3 C), 27.3, 22.6, 18.0, 14.1, 7.9; *m/z* (ESI-MS) 267.1 $(M+Na)^+$.

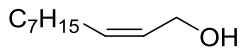
Panaxjapyne A 239. This compound is known and has been fully characterized.[99]



(*S*,*S*)-**c2** (6.0 mg, 0.01 mmol) was dissolved in HCO_2H/Et_3N 5:2 azeotropic mixture (166 mg) and ketone panaxjapynone A (24.2 mg, 0.1 mmol) in degassed CH_2Cl_2(1.0 cm^3) was injected under a nitrogen atmosphere. The mixture was stirred at rt for 1 h then quenched using sat NH_4Cl (3 cm^3), extracted with CH_2Cl_2 (3 × 15 cm^3) and the combined organic phase was dried over anhydrous $MgSO_4$, concentrated and purified by column chromatography (hexane:EtOAc 20/1-10/1) to afford panaxjapyne A **239** as a yellow oil (20.3 mg, 0.083 mmol, 85%, 96% ee by HPLC (analyze of panaxjapyne A 4-methoxybenzonate); ee determined by modified Mosher ester method was >90% ee however a more accurate value was obtained by chiral HPLC analysis). $[\alpha]_D^{28}$ +11.0 (c 0.1 in CH_3OH) 96% ee (*S*); Lit[99] $[\alpha]_D$+50.0 (c 0.02 in CH_3OH) (*S*); (found (ESI): M^+ + Na, 269.1876. $C_{17}H_{26}O$ requires M, 269.1876); ν_{max} 3330, 2958, 2854, 2256, 1460, 1012, 967, 903 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.55-5.47 (1H, m, C*H*=CH), 5.42-5.34 (1H, m, CH=C*H*), 4.38-4.33 (1H, m, *J* 6.1, C*H*OH), 3.03 (2H, d, *J* 6.9, =HCCH_2C≡), 2.02 (2H, q, *J* 7.1, =CHCH_2), 1.79-1.69 (3H, m, CHOHCH_2 and OH), 1.40-1.22 (10H, m, CH_2CH_2CH_2CH_2C$H_2$$CH_3$), 1.01 (3H, t, *J* 7.4, CHOHCH_2CH_3), 0.88 (3H, t, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 133.0, 122.0, 79.6, 76.7, 69.9, 64.1 (2C), 31.8, 30.7, 29.25, 29.20, 29.17, 27.2, 22.7, 17.7, 14.1, 9.3; *m/z* (ESI-MS) 269.1 $(M+Na)^+$. HPLC separation conditions: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 97:03, 0.6 cm^3/min, T = 30 °C. Retention times: (major - *S*) 10.9 min, (minor - *R*) 13.7 min. Ee was determined to be 96% by analysis of racemic panaxjapyne A and panaxjapyne A 4-methoxybenzonate.



(Z)-Dec-2-ene-1-ol 232. This compound is known and has been fully characterized.[147a]



A mixture of quinoline (152 mg, 1.18 mmol,) and Lindlar's catalyst (108 mg, 10% w/w) in EtOAc (30 cm^3) was stirred at rt for 1 h. A solution of 2-decyn-1-ol (1.07 g, 7.0 mmol) in EtOAc (10 cm^3) was injected. After the mixture had beendegassed once, a H_2 balloon was attached and then the mixture was stirred vigorously for 9 h. The reaction mixture was then filtered through a plug of Celite, concentrated and purifiedby column chromatography (hexane/EtOAc=3:1) to afforded the alkene **232** as a colourless oil (1.08 g, 7.0 mmol, 99%, Z/E=14/1). δ_H (400 MHz, $CDCl_3$) 5.63-5.51 (2H, m, CH=CH), 4.19 (2H, d, *J* 6.1, C*H*$_2$OH), 2.07 (2H, q, *J* 7.0, =CHC*H*$_2$), 1.60 (1H, br, OH), 1.40-1.20 (10H, br, (C*H*$_2$)$_5$CH$_3$), 0.88 (3H, t, *J* 7.0, CH_3).

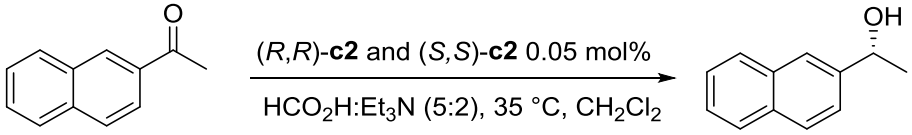
(Z)-1-Bromodec-2-ene 233. This compound is known and has been fully characterized.[147a]

At 0 °C, under a N_2 atmosphere, a solution of (Z)-dec-2-ene-1-ol **232**(1.08 g, 7.0 mmol,) and Ph_3P (2.20 g, 8.1 mmol) in dry CH_2Cl_2 (28 cm^3) was treated with CBr_4 (2.82 g, 8.5 mmol, in 10 cm^3 CH_2Cl_2) solution dropwise. After the addition was complete, the mixture waswarmed to room temperature and stirred for 1.5 h. Solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (pure hexane) to afforded pure bromide **233** as a colourless oil (1.20 g, 5.5 mmol, 78%). δ_H (400 MHz, $CDCl_3$) 5.78-5.69 (1H, m, =C*H*CH$_2$OH), 5.63-5.57 (1H, m, =CH), 4.00

(2H, d, *J* 8.2, C*H*$_2$OH), 2.13 (2H, qd, *J* 7.4 1.4, =CHC*H*$_2$), 1.43-1.23 (10H, br, (C*H*$_2$)$_5$CH$_3$), 0.86 (3H, t, *J* 6.5, CH$_3$).

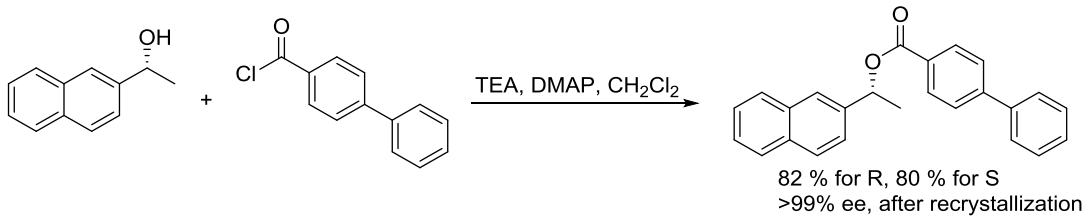
3.22. Synthesis of Chiral 1-(2'-Naphthyl)ethyl-(4-phenylbenzoate).

Chiral 1-(2'-Naphthyl)ethanol 241. This compound is known and has been fully characterized.



(*R*,*R*)-**c2** or (*S*,*S*)-**c2** (0.6 mg, 1.0 × 10^{-3} mmol) was dissolved in HCO$_2$H/Et$_3$N 5:2 azeotropic mixture (840 mg, 0.59 cm^3) and 2-acetonaphthone **240** (340 mg, 2.0 mmol) in degassed CH$_2$Cl$_2$ (2.0 cm^3)was injected under a nitrogen atmosphere. The mixture was stirred at 35 °C for 48 h then saturated aqueous NaHCO$_3$ (10 cm^3) was added. The reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 20 cm^3), dried over anhydrous MgSO$_4$, concentrated and purified by silica gel column chromatography (eluent hexane/EtOAc=5:1) to give chiral 1-(2'-naphthyl)ethanol **241** as a white solid (334.4 mg, 1.94 mmol, 97%, 93% ee for *R*-**241**), (331.4 mg, 1.93 mmol, 96%, 93% ee for *S*-**241**). $[\alpha]_D^{24}$ + 37.8 (c 0.5 in EtOH), 93% ee (*R*). (Lit[155a] $[\alpha]_D^{25}$ + 41.2 (c 0.50 in EtOH), 95% ee (*R*); Lit[155b] $[\alpha]_D^{25}$ + 36.3 (c 0.58 in EtOH), 85% ee (*R*), δ_H (400 MHz, CDCl$_3$) 7.84-7.80 (4H, m, Ar), 7.51-7.44 (3H, m, Ar), 5.06 (1H, qd, *J* 6.5, 3.6, CH), 1.93 (1H, brs, OH), 1.57 (3H, d, *J* 6.5 CH$_3$). HPLC separation conditions: CHIRALPAK IB column (250 mm x 4.6 mm) hexane:*i*-PrOH 96:4, 0.7 cm^3/min, T = 30 °C. Retention times, (*S*) 18.1 min, (*R*) 19.2 min. GC condition: Chrompaccyclodextrin-β-236M-19 50m, Carrier = hydrogen, T = 155 °C, P = 15 psi, Retention time for *R* isomer 60.8 min., Retention times for *S* isomer 62.4 min.

Chiral 1-(2'-naphthyl)ethyl-(4-phenylbenzoate) 243. This compound is novel.



To a solution of chiral 1-(2'-naphthyl)ethan-1-ol **241** (294 mg, 1.71 mmol) and 4-phenylbenzoyl chloride (555 mg, 2.56 mmol) in CH_2Cl_2 (40 cm^3), DMAP (catalytic amount, 5 mg) and triethylamine (518 mg , 5.13 mmol) in CH_2Cl_2 (15 cm^3) wereadded dropwise at 0 °C. The reaction mixture was allowed to warm up to room temperature overnight and sat $NaHCO_3$ (30 cm^3) was added. After stirring for 2 h, the organic phase was separated and further extracted with CH_2Cl_2 (2 × 40 cm^3). The combined organic phase was washed with brine (10 cm^3), dried over anhydrous $MgSO_4$,concentrated and purified by silica gel column chromatography (eluent hexane/CH_2Cl_2/EtOAc=10:1:0.4) to give 1-(2'-naphthyl)ethyl-(4-phenylbenzoate) **243** as a white solid (501 mg, 1.42 mmol, 82 % for *R*, 480 mg, 1.36 mmol, 80 % for *S*). $[\alpha]_D^{32}$ - 170.5 (c 0.5 in $CHCl_3$) >99% ee (*R*). $[\alpha]_D^{32}$ + 169.0 (c 0.6 in $CHCl_3$) >99% ee (*S*). Recrystallized samples were used for optical rotation measurements. MP 110 °C; (found (ESI): M^+ + Na, 375.1356. $C_{25}H_{20}O_2$ requires M, 375.1355); ν_{max} 1704, 1283, 1275, 745 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.18-8.15 (2H, m, Ar), 7.90-7.81 (4H, m, Ar), 7.67-7.58 (5H, m, Ar), 7.50-7.37 (5H, m, Ar), 6.32 (1H, d, *J* 6.6, CH), 1.77 (3H, q, *J* 6.6, CH_3); δ_C (100 MHz, $CDCl_3$) 165.8, 145.7, 140.1, 139.2, 133.3, 133.1, 130.2, 129.3, 129.0, 128.5, 128.2, 128.1, 127.7, 127.3, 127.1, 126.3, 125.1, 125.1, 124.1, 73.1, 22.4. HPLC separation conditions: CHIRALPAK IB column (250 mm x 4.6 mm) hexane:*i*-PrOH 98:2, 0.6 cm^3/min, T = 30 °C. Retention times, (*R*) 12.8 min and (*S*) 23.1 min. A sample of the racemic alcohol was prepared by $NaBH_4$ reduction of 2-acetonaphthone and conversion to the ester for HPLC analysis.

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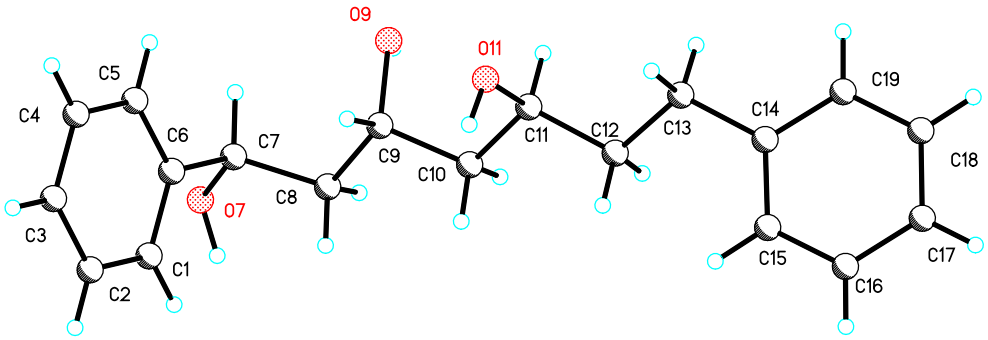
5. Appendix: Selected Experimental Data

5.1. X-ray Crystallography Data of Yashabushitriol

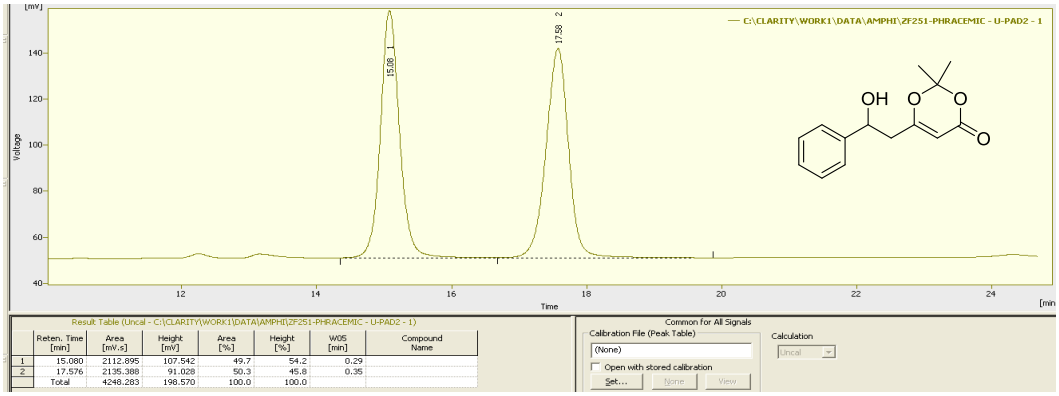


Crystal data: $C_{19}H_{24}O_3$, M = 300.38, Monoclinic, space group P2(1) a=9.32711(10), b = 5.70755(6), c = 15.13134(16) A, α= 90 deg., β= 91.5550(10) deg., γ= 90 deg., U =805.220(15) $Å^3$ (by least squares refinement on 5461 reflection positions), T =150(2)K, lambda = 1.54184 Å, Z = 2, D(cal) = 1.239 Mg/m^3, F(000)=324. Mu(MoK-α) = 0.655 mm^{-1}. Crystal character: colourless block. Crystal dimensions 0.45 x 0.20 x 0.12 mm.

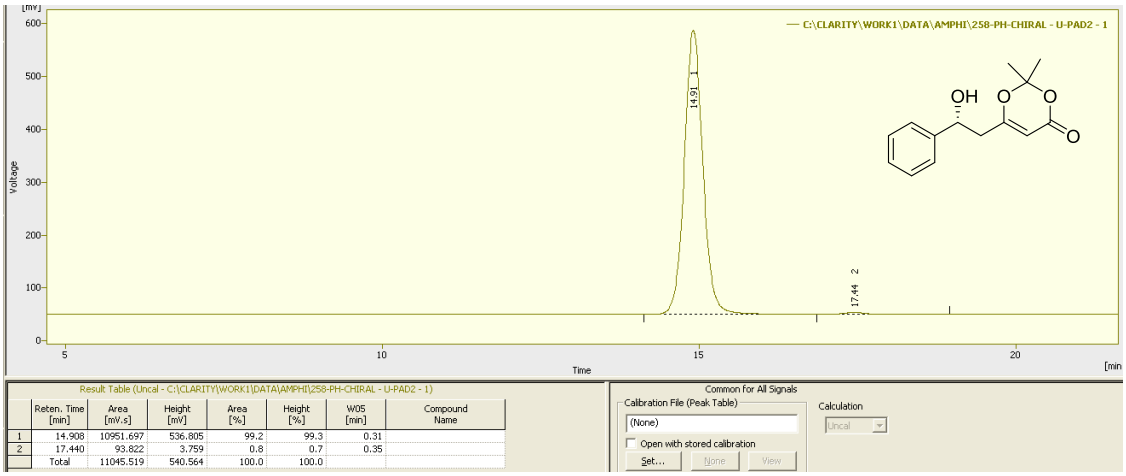
5.2. HPLC Results of Typical Compounds

HPLC separation conditions for compound *R*-**114**: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 90:10, 1.0 cm^3/min, T = 30 °C. Retention times: (major - *R*) 14.9 min, (minor - *S*) 17.3 min.

Racemic **114**



Chiral *R*-**114**, S/C=1000/1

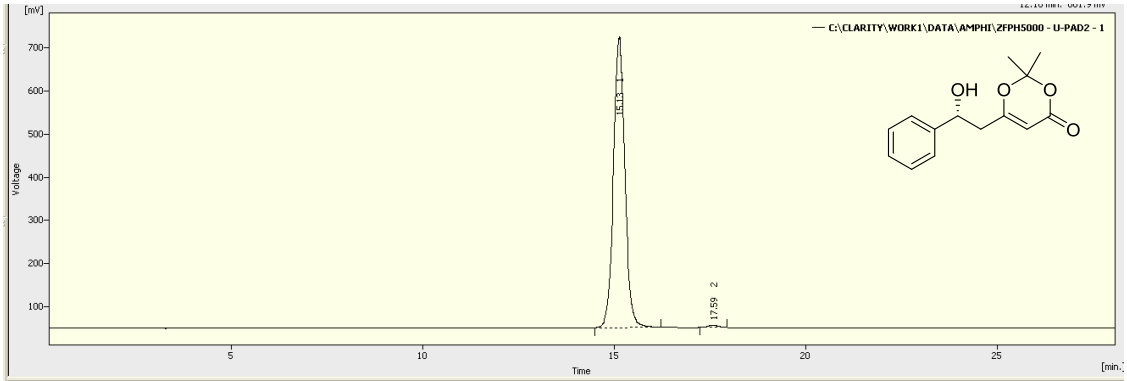


Result Table (Uncal - C:\CLARITY\WORK1\DATA\AMPHI\258-PH-CHIRAL - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	14.908	10951.697	536.805	99.2	99.3	0.31	
2	17.440	93.822	3.759	0.8	0.7	0.35	
	Total	11045.519	540.564	100.0	100.0		

Common for All Signals
Calibration File (Peak Table)
(None)
Open with stored calibration
Set... None View
Calculation
Uncal

Chiral *R*-**114**, S/C=5000/1



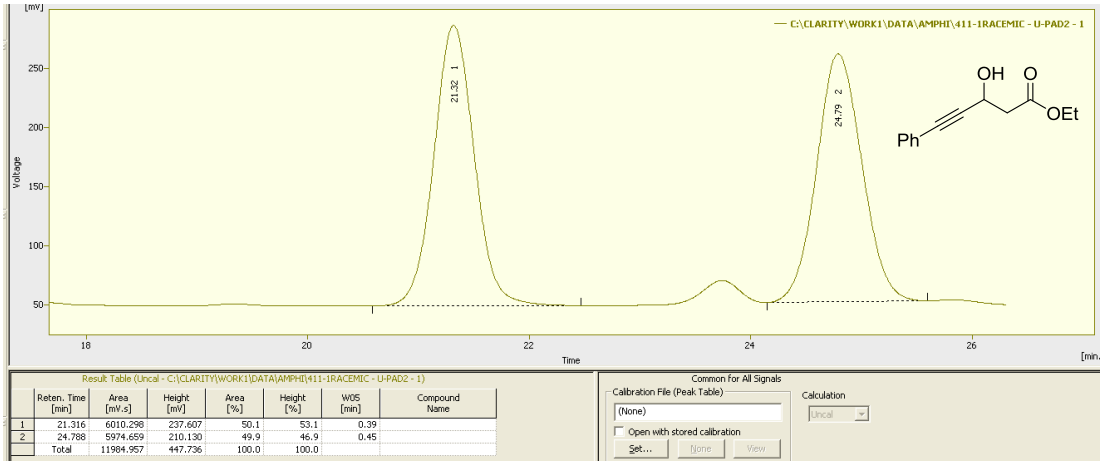
Result Table (Uncal - C:\CLARITY\WORK1\DATA\AMPHI\ZFPH5000 - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	15.132	14026.413	674.573	99.3	99.3	0.32	
2	17.588	96.147	4.830	0.7	0.7	0.32	
	Total	14122.560	679.403	100.0	100.0		

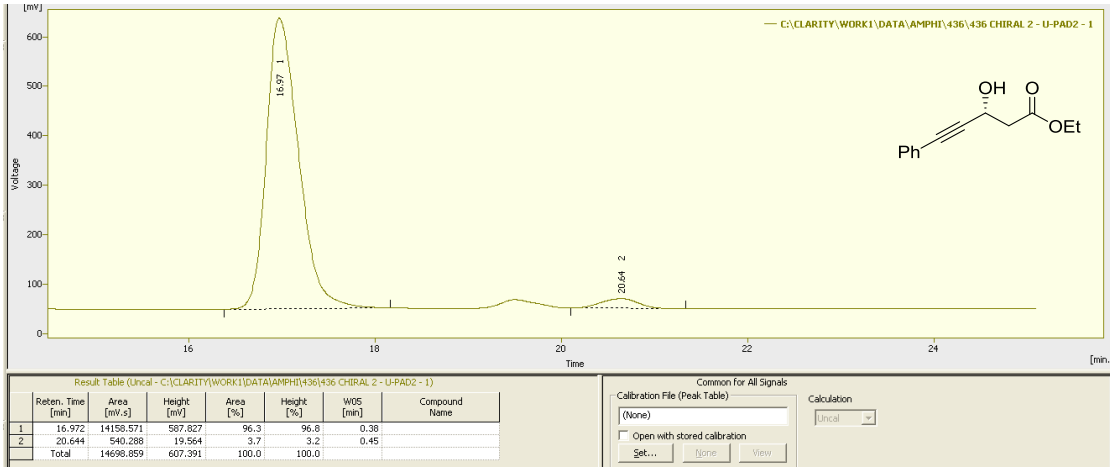
Common for All Signals
Calibration File (Peak Table)
(None)
Open with stored calibration
Set... None View
Calculation
Uncal

HPLC separation conditions for compound *R*-**171**: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:5, 0.6 cm^3/min, T = 30 °C, 254 nm UV.

Racemic **171**.

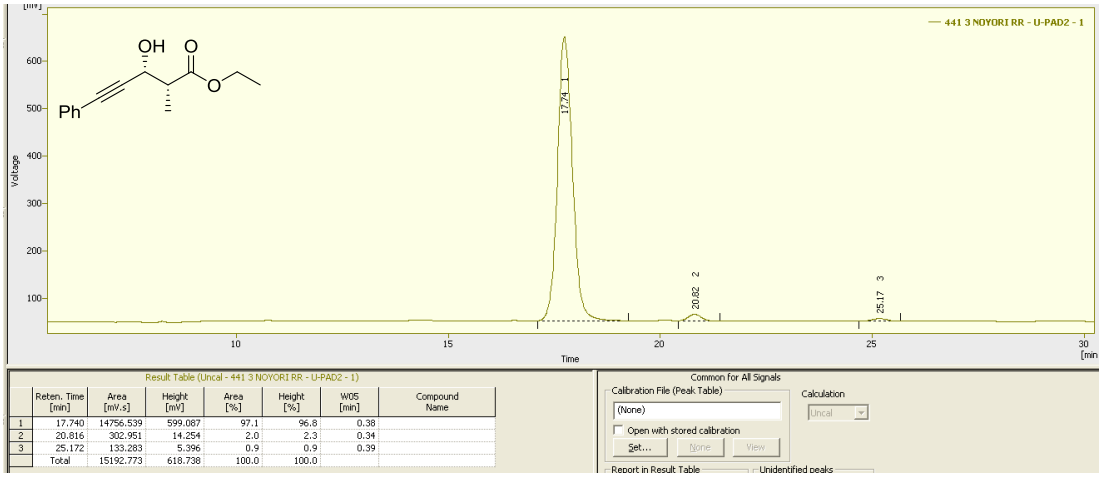


Chiral *R*-**171**.

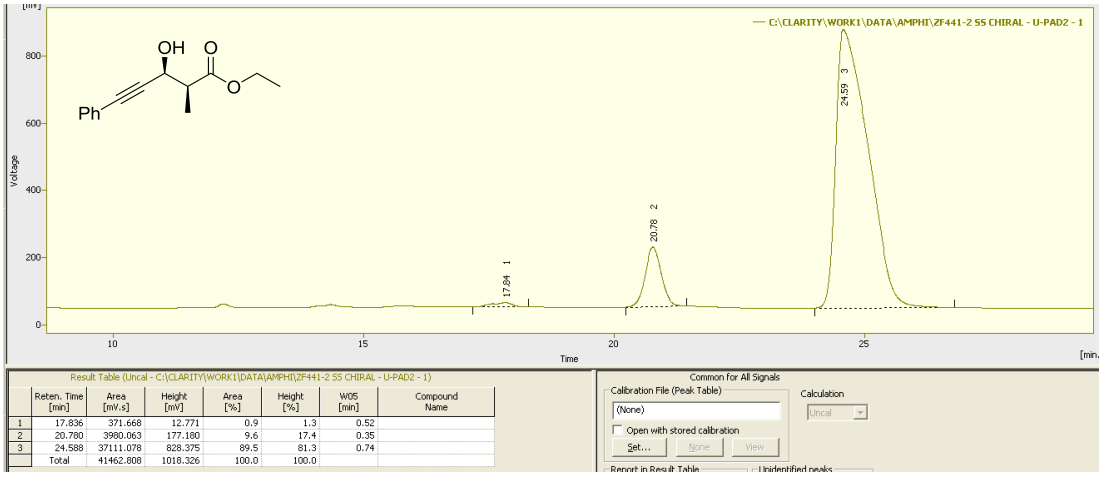


HPLC separation conditions for compound **172**: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:4, 0.5 cm^3/min, T = 30 °C, 254 nm UV.

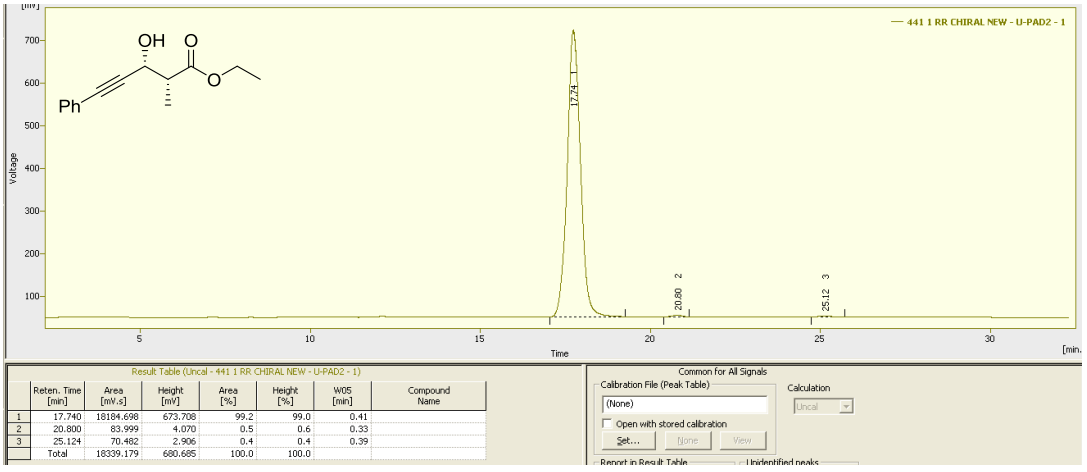
Chiral (2*R*, 3*R*)-**172** prepared by using catalyst (*R*,*R*)-**c1**.



Chiral (2*S*, 3*S*)-**172** prepared by using catalyst (*S*,*S*)-**c2**

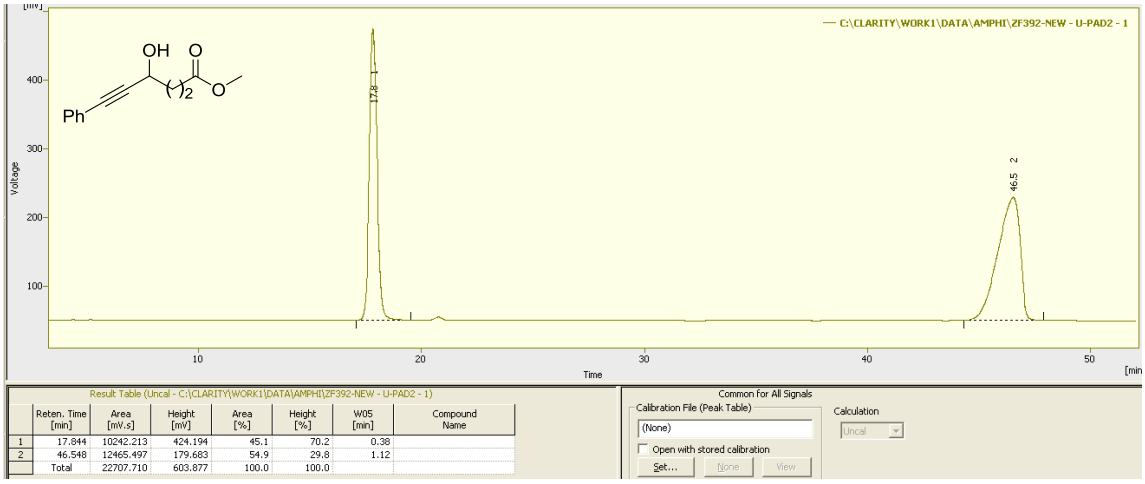


Chiral (2*R*, 3*R*)-**172** prepared by using catalyst (*R*,*R*)-**c2**.

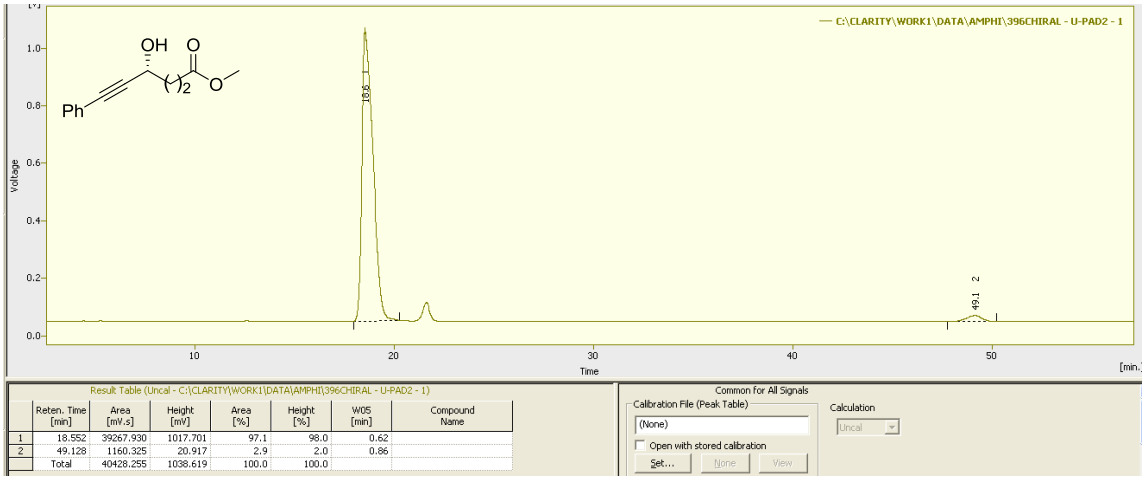


HPLC separation conditions for compound *R*-**184**: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:5, 0.8 cm^3/min, T = 30 °C, 254 nm UV.

Racemic **184**.

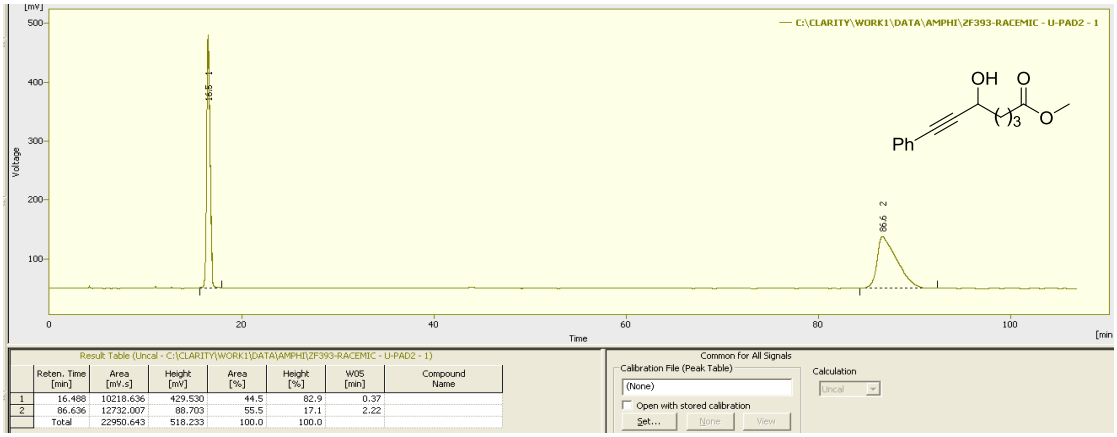


Chiral *R*-**184**.

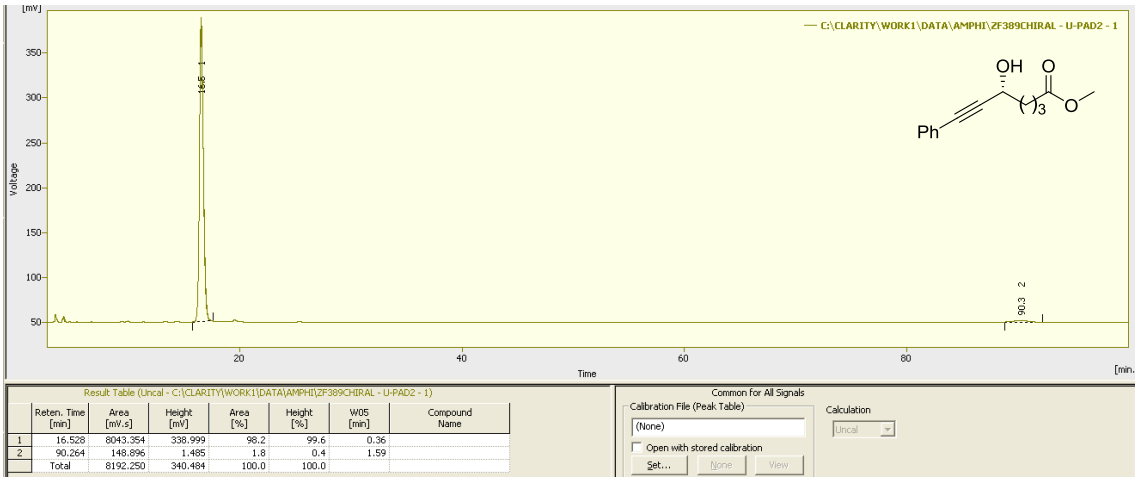


HPLC separation conditions for compound *R*-**188**: CHIRALPAK IB column (250 mm × 4.6 mm), hexane:*i*-PrOH 95:5, 0.8 cm^3/min, T = 30 °C, 254 nm UV.

Racemic **188**.

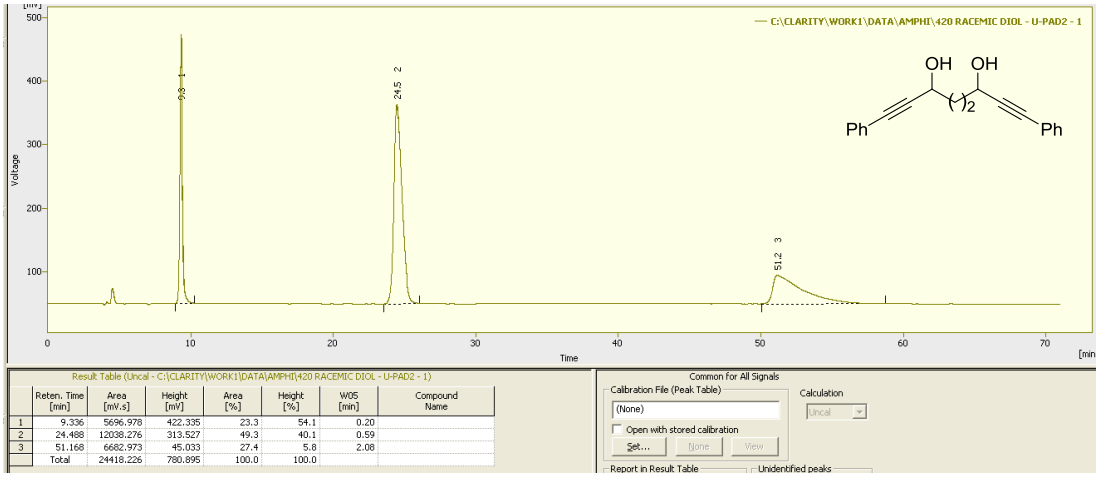


Chiral *R*-**188**.

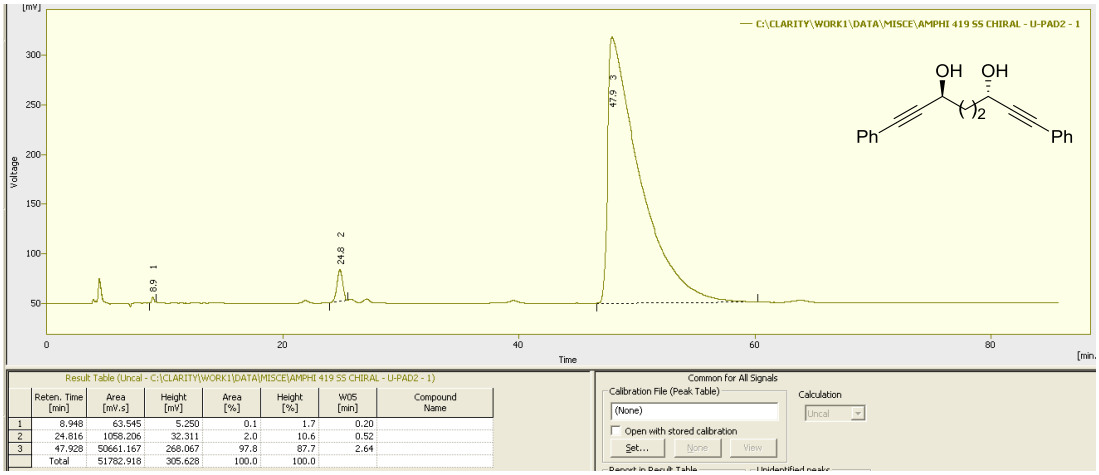


HPLC separation conditions for compound **202**: CHIRALPAK IB column (250 mm × 4.6 mm), hexane: *i*-PrOH 80:20, 0.8 cm^3/min, T = 30 °C, 254 nm UV.

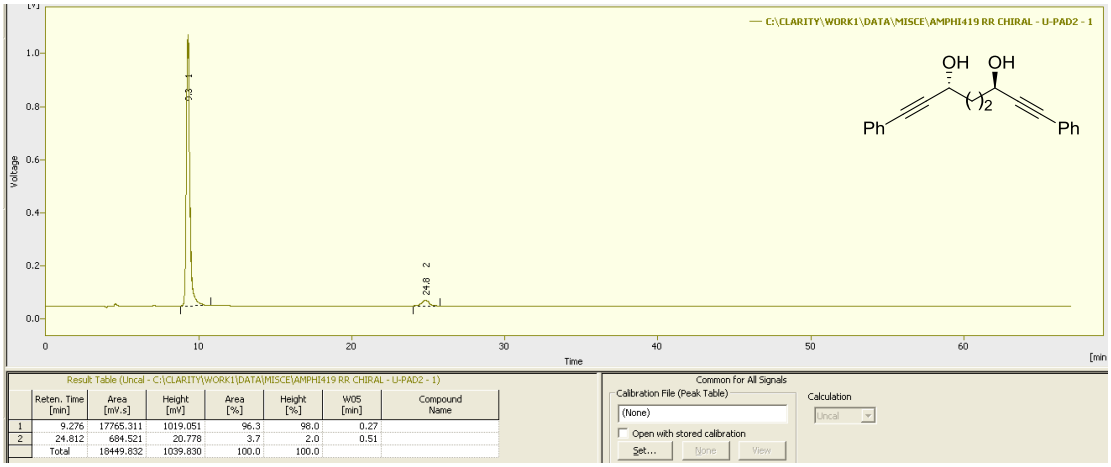
Racemic + *meso* **202**.



Chiral *S,S*-**202**.

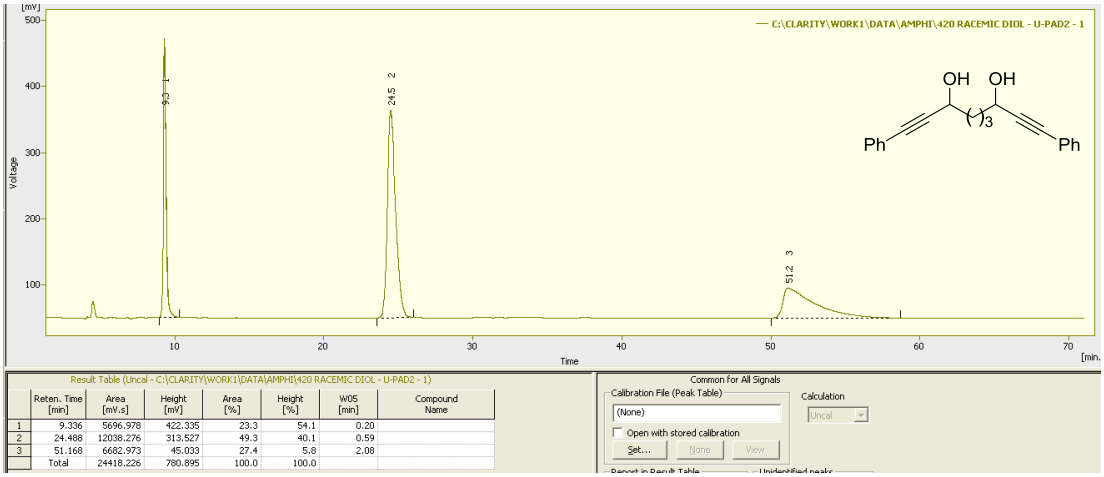


Chiral *R,R*-**202**.

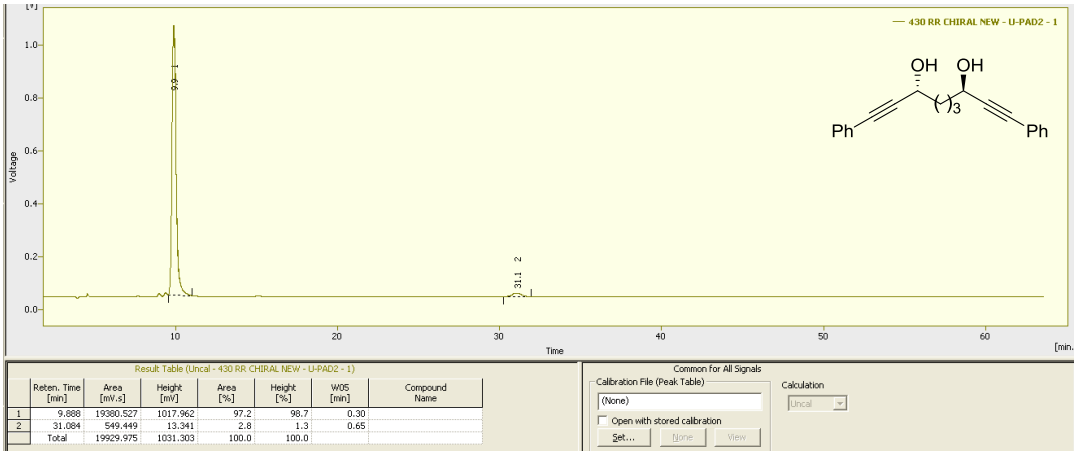


HPLC separation conditions for compound **205**: CHIRALPAK IB column (250 mm × 4.6 mm), hexane: *i*-PrOH 80:20, 0.8 cm^3/min, T = 30 °C, 254 nm UV.

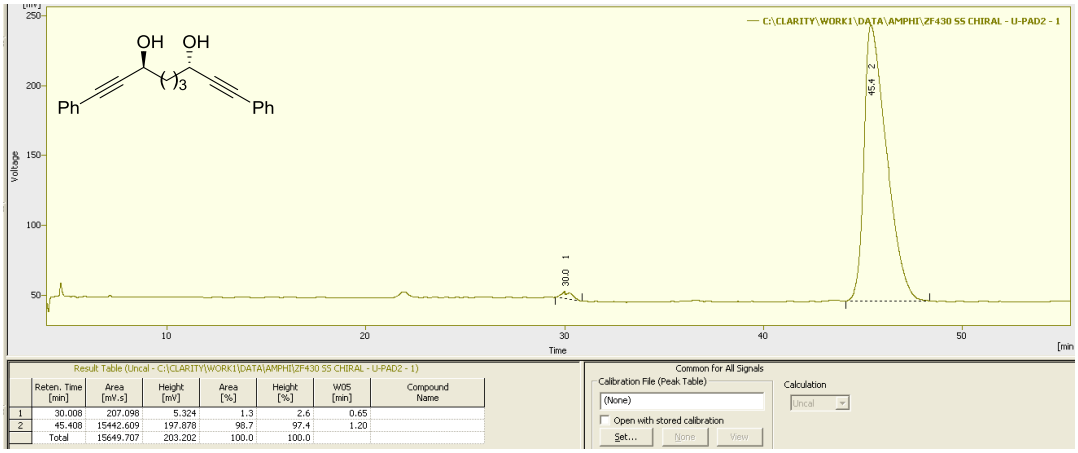
Racemic + *meso* **205**



Chiral *R,R*-**205**.

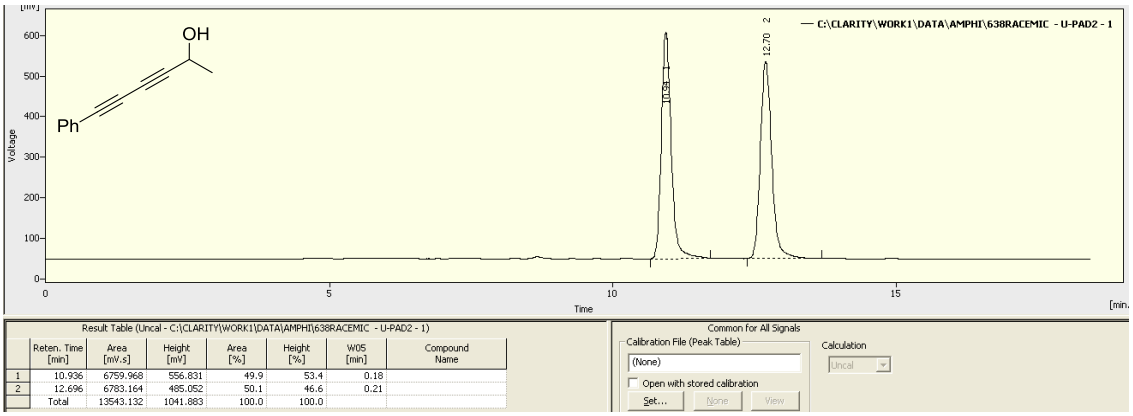


Chiral *S,S*-**205**.



HPLC separation conditions for compound *S*-**215**: CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 96:04, 0.8 cm^3/min, T = 30 °C, 210 nm UV.

Racemic **215**.

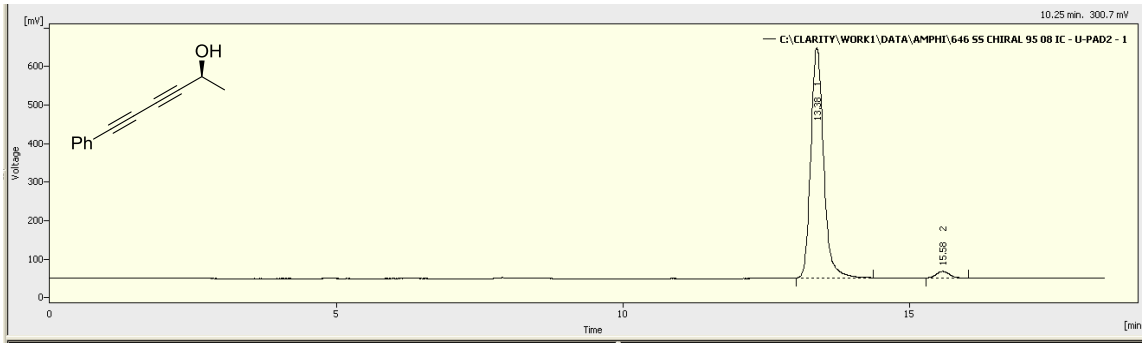


Result Table (Uncal - C:\CLARITY\WORK1\DATA\AMPHI\638RACEMIC - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	10.936	6759.968	556.831	49.9	53.4	0.18	
2	12.696	6783.164	485.052	50.1	46.6	0.21	
	Total	13543.132	1041.883	100.0	100.0		

Common for All Signals
Calibration File (Peak Table)
(None)
Open with stored calibration
Set... None View
Calculation
Uncal

Chiral *S*-**215**.



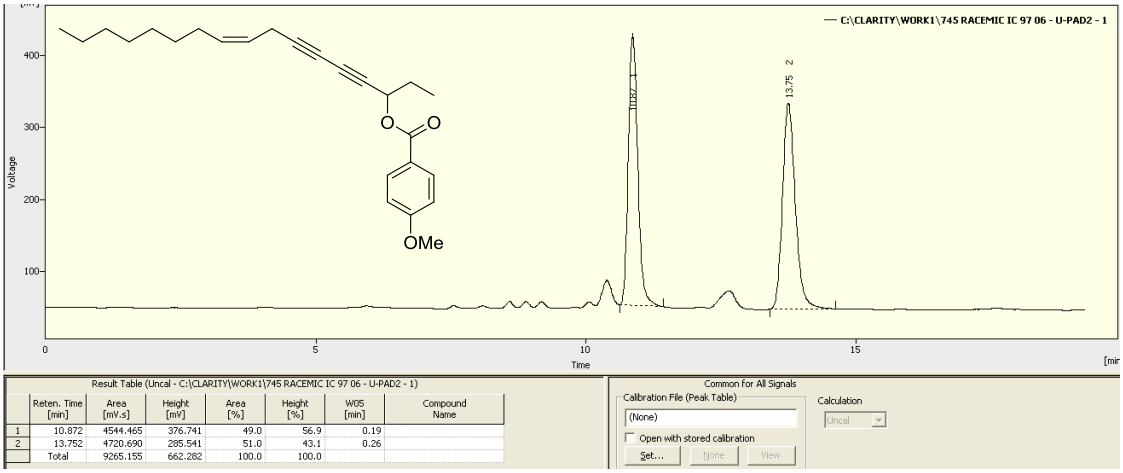
Result Table (Uncal - C:\CLARITY\WORK1\DATA\AMPHI\646 SS CHIRAL 95 08 IC - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	13.380	9302.542	597.617	97.1	97.2	0.24	
2	15.576	273.344	17.185	2.9	2.8	0.25	
	Total	9575.886	614.802	100.0	100.0		

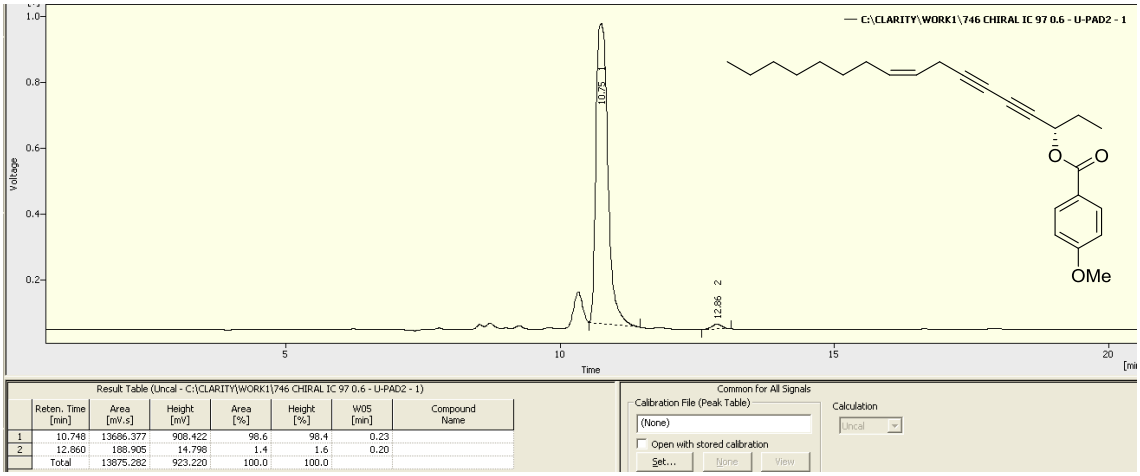
Common for All Signals
Calibration File (Peak Table)
(None)
Open with stored calibration
Set... None View
Calculation
Uncal

HPLC separation conditions for compound panaxjapyne A 4-methoxybenzonate (reduced by (*S*,*S*)-**c2**) : CHIRALPAK IC column (250 mm × 4.6 mm), hexane:*i*-PrOH 97:03, 0.6 cm^3/min, T = 30 °C, 210 nm UV.

Racemic

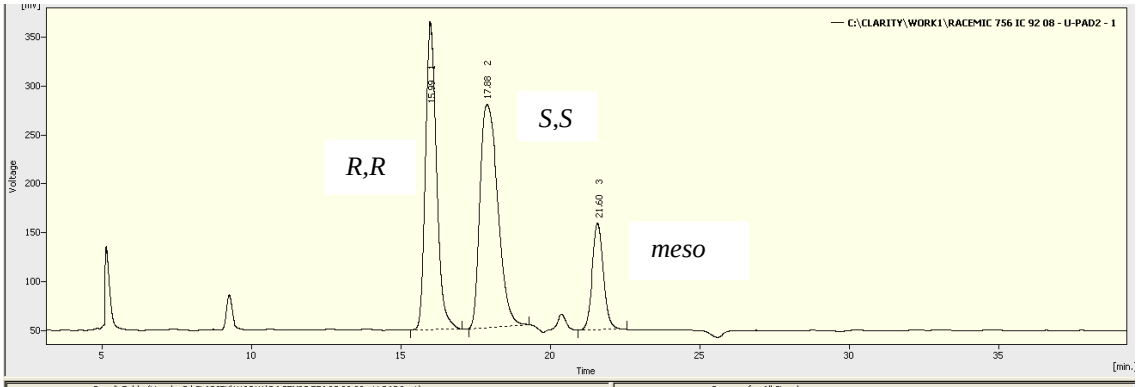


Chiral



(-)-Yashabushidiol B **213**; CHIRALPAK IC column (250 mm x 4.6 mm), hexane:*i*-PrOH 92:8, 0.8 cm^3/min, T = 30 °C, 210 nm UV.

Racemic **213** (from ^{1}H NMR the racemic *anti*-diol sample contain 15 % of *meso*-diol)

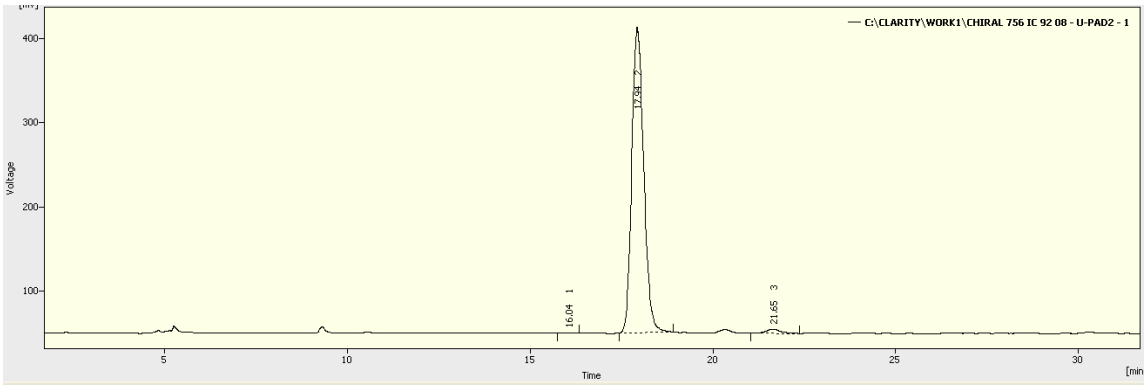


Result Table (Uncal - C:\CLARITY\WORK1\RACEMIC 756 IC 92 08 - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	15.992	8403.414	315.500	40.5	48.3	0.42	
2	17.880	9495.151	228.249	45.8	34.9	0.67	
3	21.596	2852.689	109.362	13.7	16.7	0.40	
	Total	20751.254	653.111	100.0	100.0		

Common for All Signals
Calibration File (Peak Table)
(None)
Open with stored calibration
Set... None View
Calculation
Uncal

(-)-Yashabushidiol B **213**.

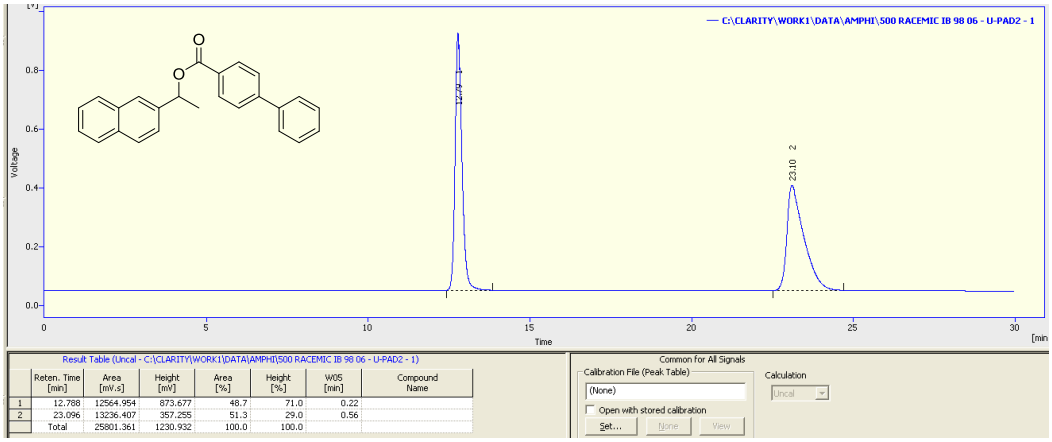


Result Table (Uncal - C:\CLARITY\WORK1\CHIRAL 756 IC 92 08 - U-PAD2 - 1)

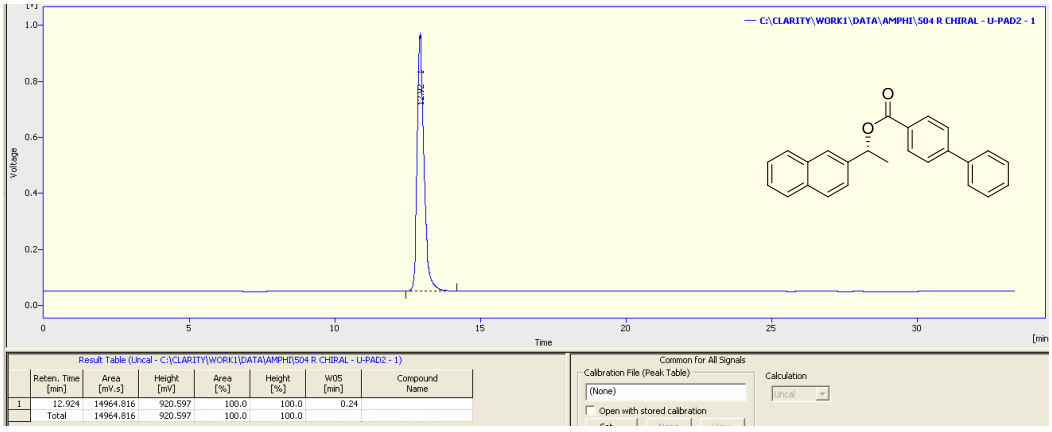
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	16.044	13.517	0.744	0.2	0.2	0.30	
2	17.936	8227.232	363.266	98.2	98.5	0.35	
3	21.648	135.478	4.775	1.6	1.3	0.41	
	Total	8376.227	368.786	100.0	100.0		

Common for All Signals
Calibration File (Peak Table)
(None)
Open with stored calibration
Set... None View
Calculation
Uncal
Report in Result Table
Unidentified peaks

Racemic **243**; HPLC separation conditions: CHIRALPAK IB column (250 mm x 4.6 mm) hexane:*i*-PrOH 98:2, 0.6 cm^3/min, T = 30 °C. Retention times, (*R*) 12.8 min and (*S*) 23.1 min.

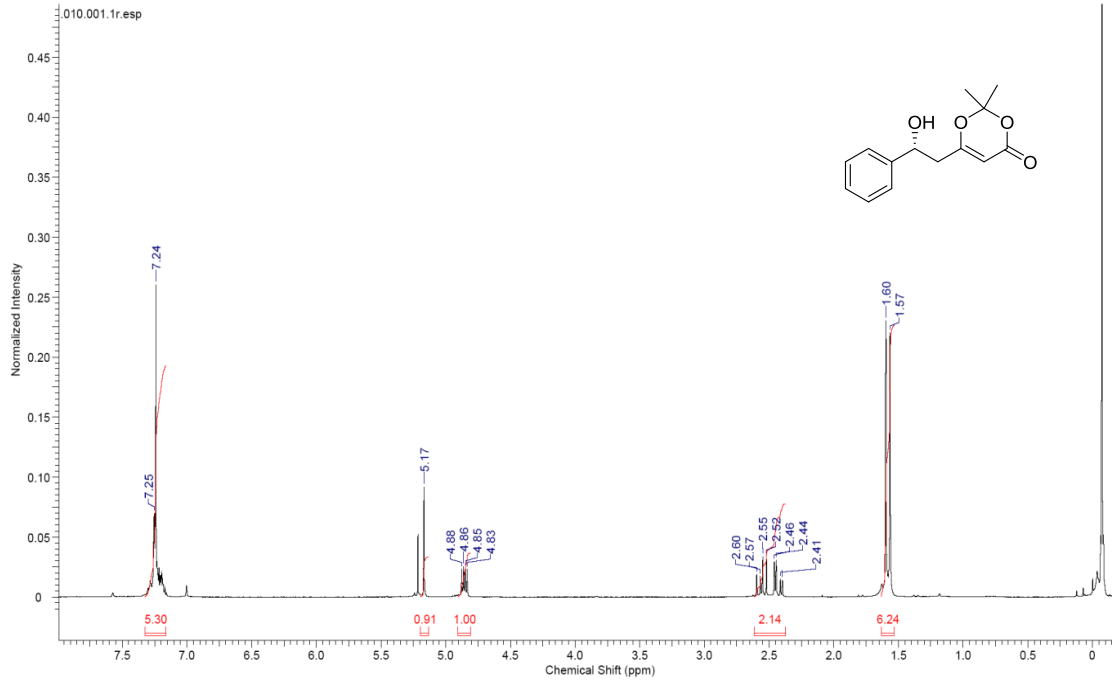


Chiral *R*-**243**.

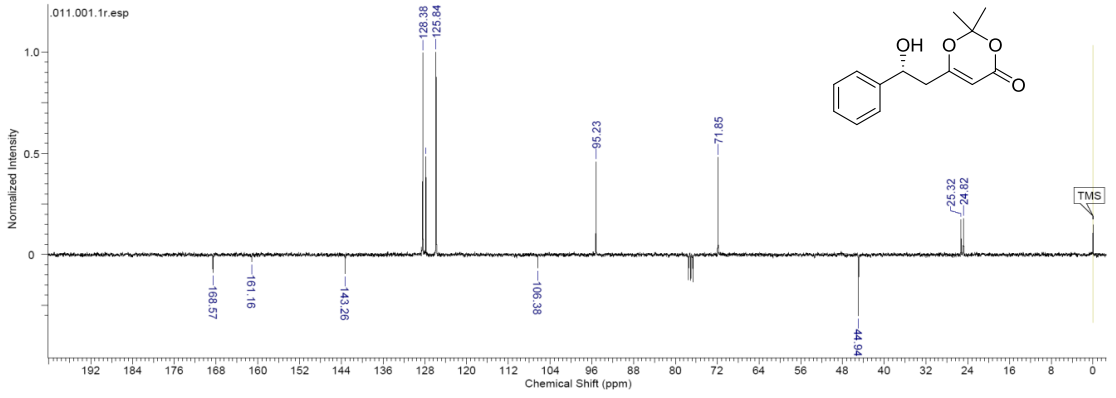


5.3. ^{1}H and ^{13}C NMR Spectra of Typical Compounds

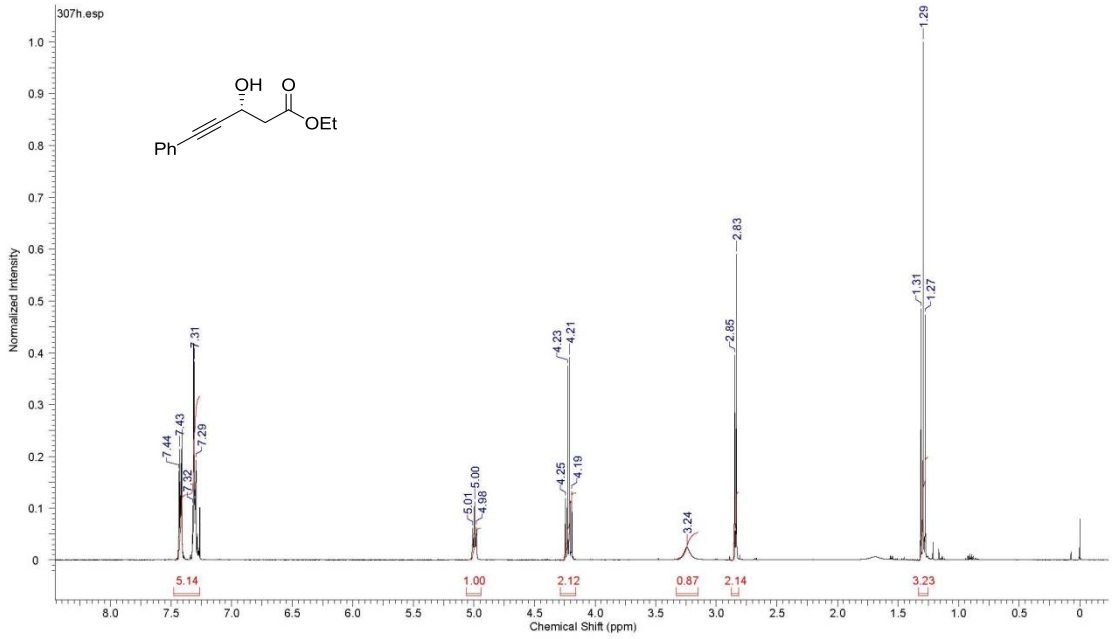
^{1}H NMR of *R*-**114**.



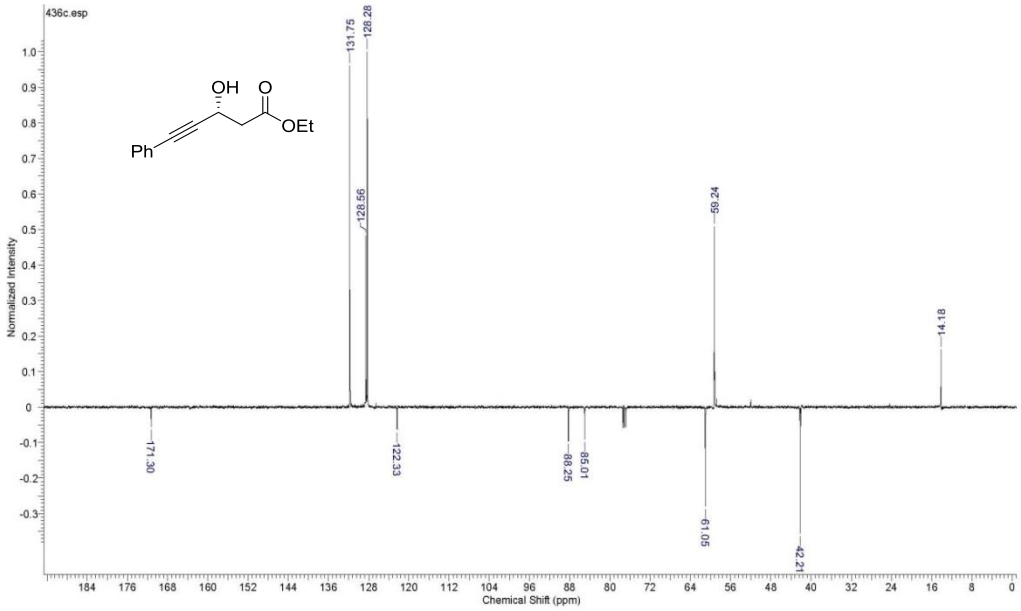
^{13}C NMR of *R*-**114**.



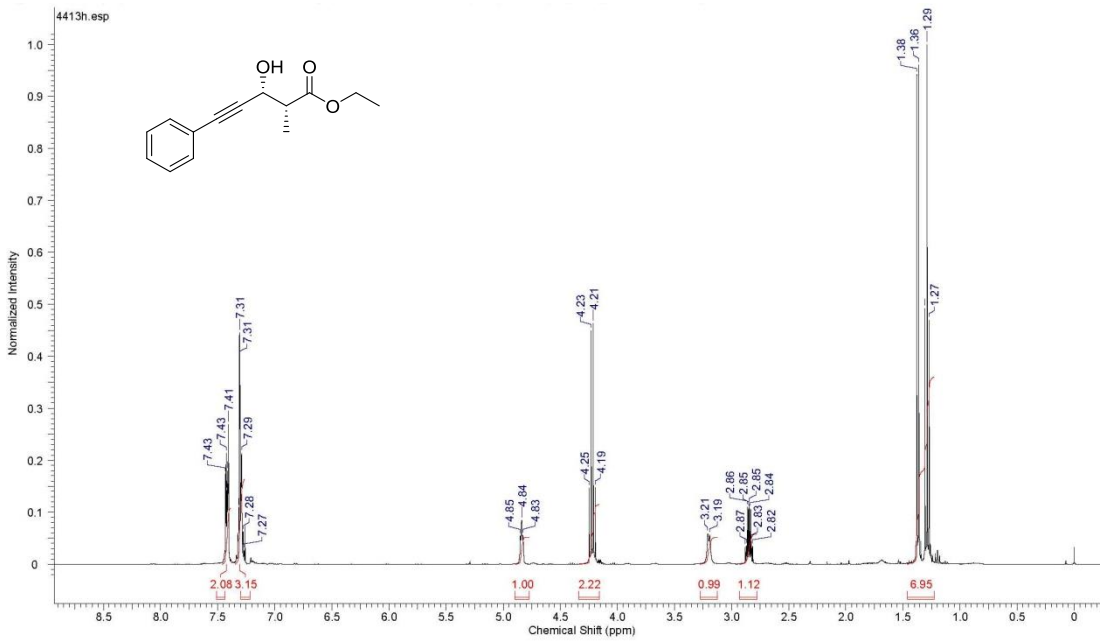
^{1}H NMR of *R*-**171**.



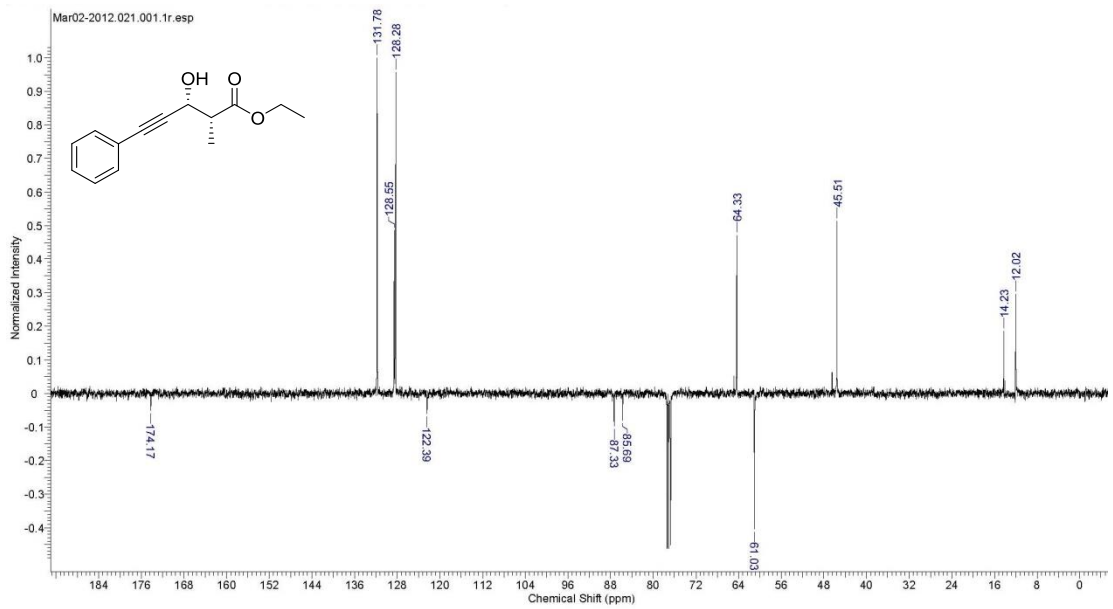
^{13}C NMR of *R*-**171**.



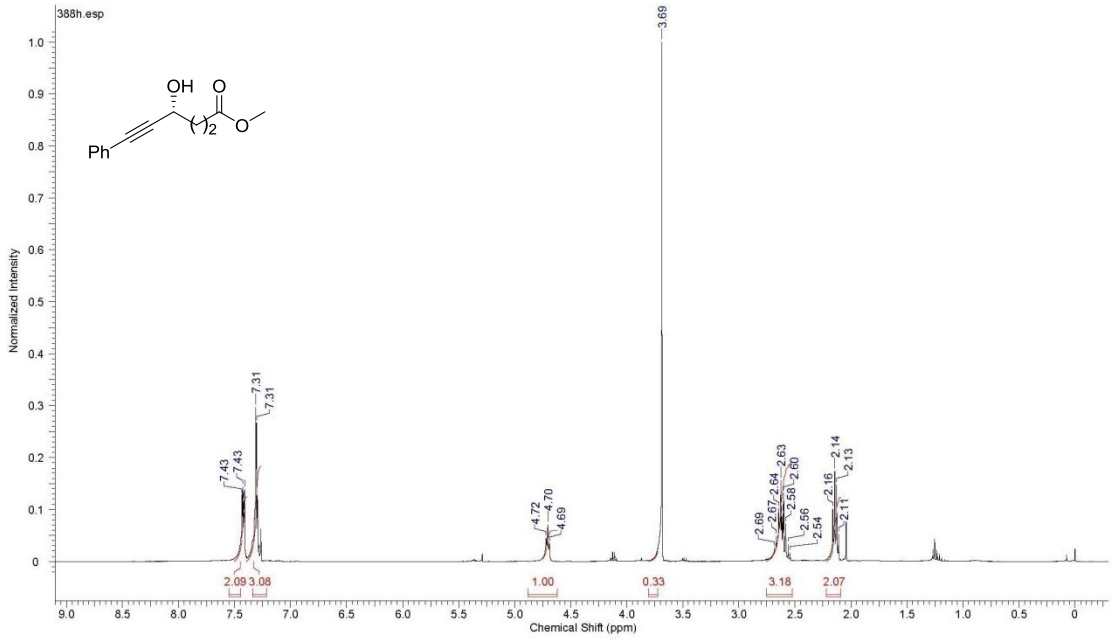
^{1}H NMR of (2*R*, 3*R*)-**172**.



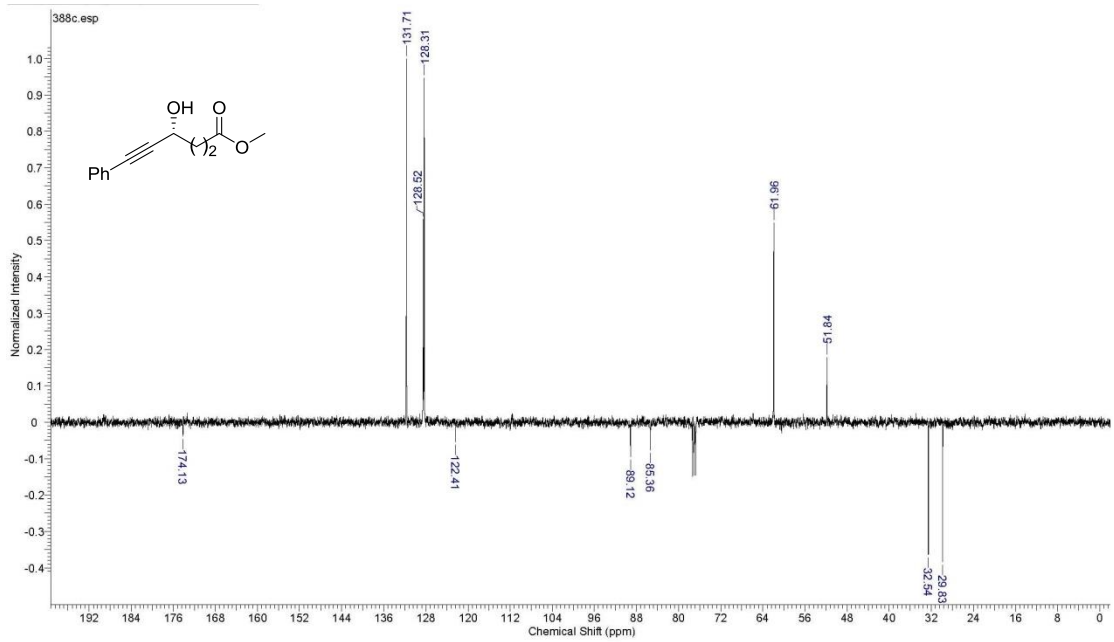
^{13}C NMR of (2*R*, 3*R*)-**172.**



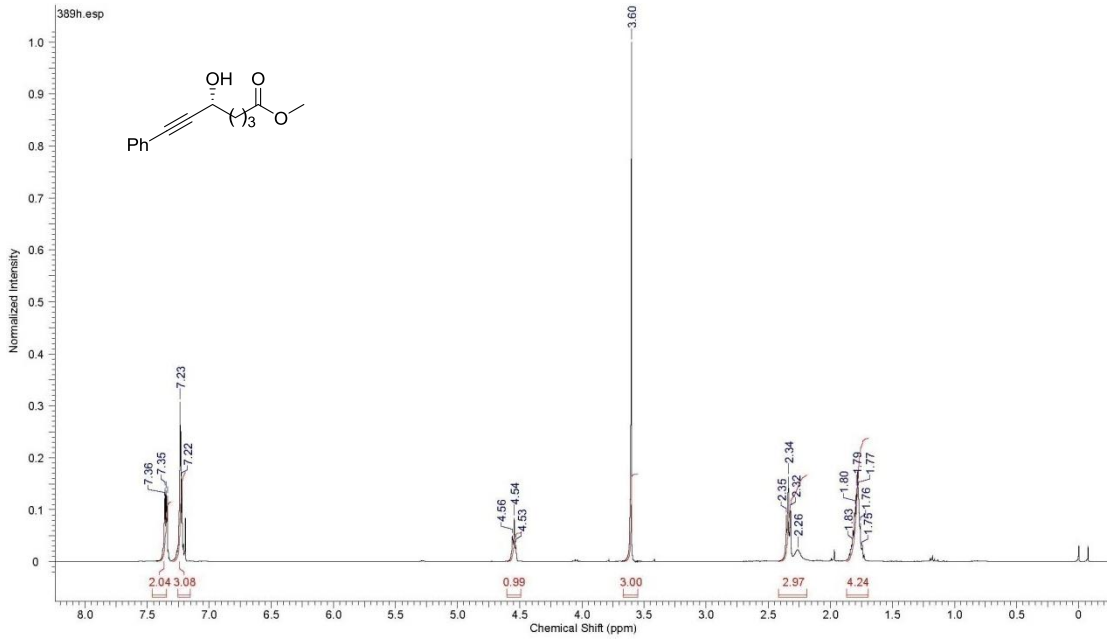
^{1}H NMR of *R*-**184**.



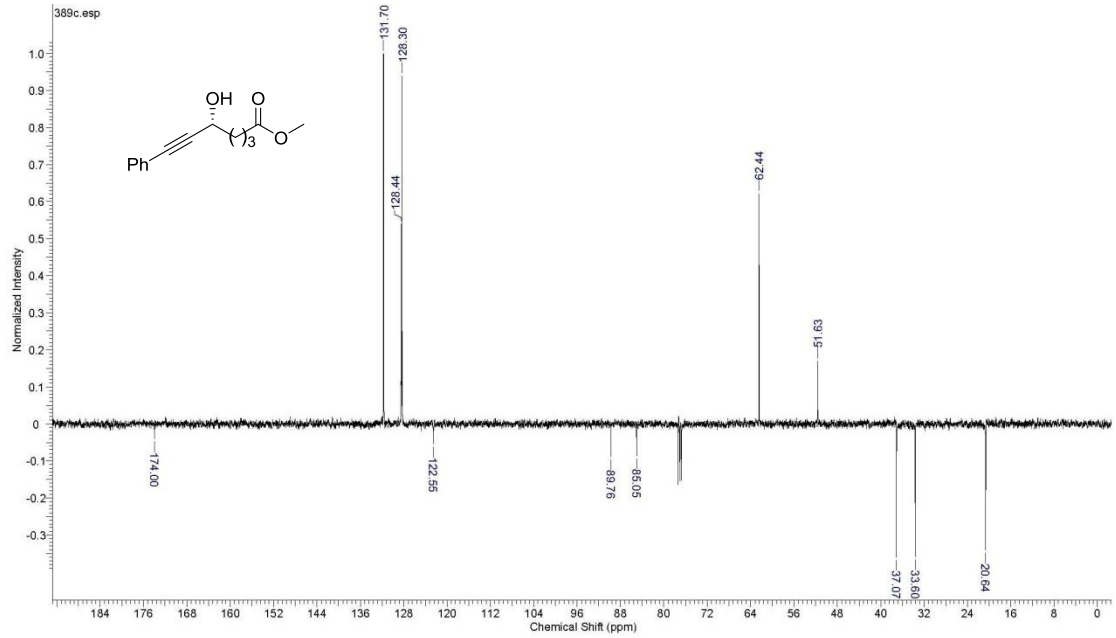
^{13}C NMR of *R*-**184**.



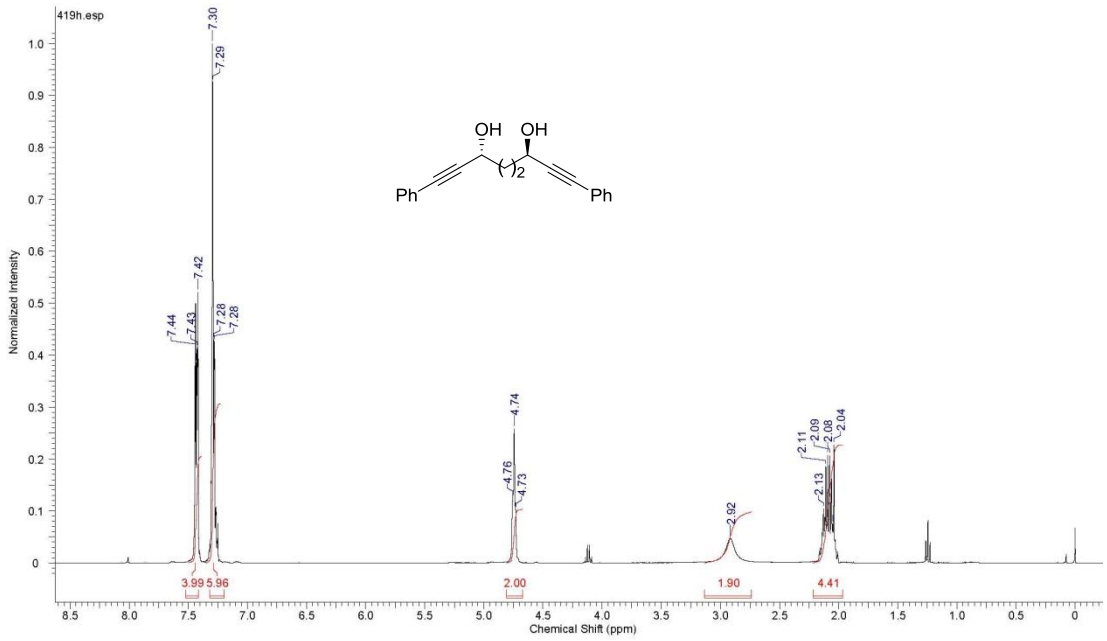
^{1}H NMR of *R*-**188**.



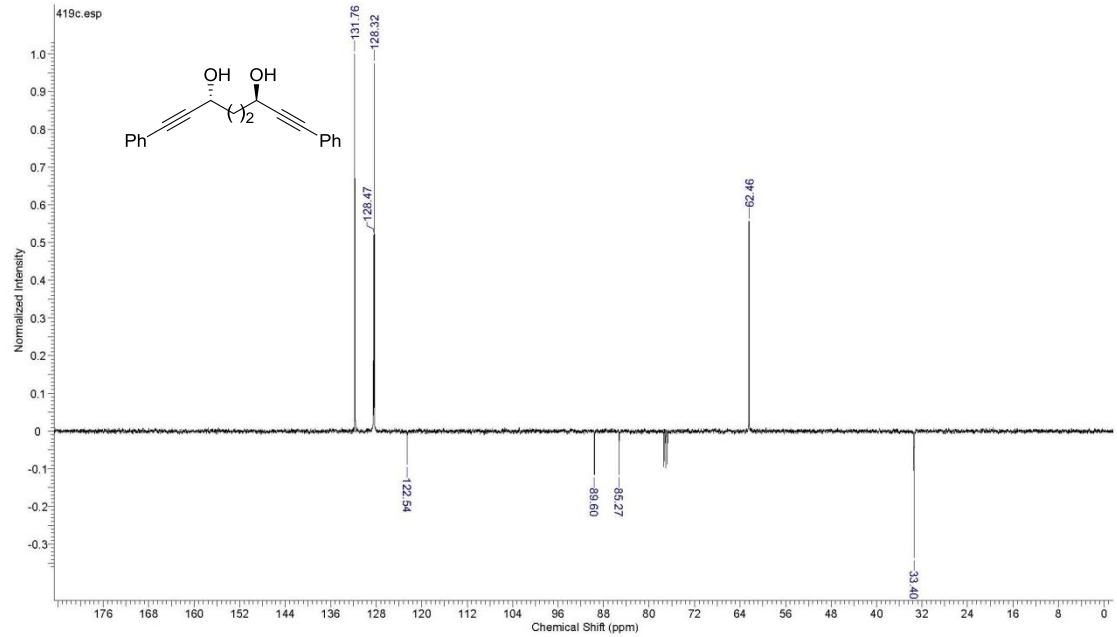
^{13}C NMR of *R*-**188**.



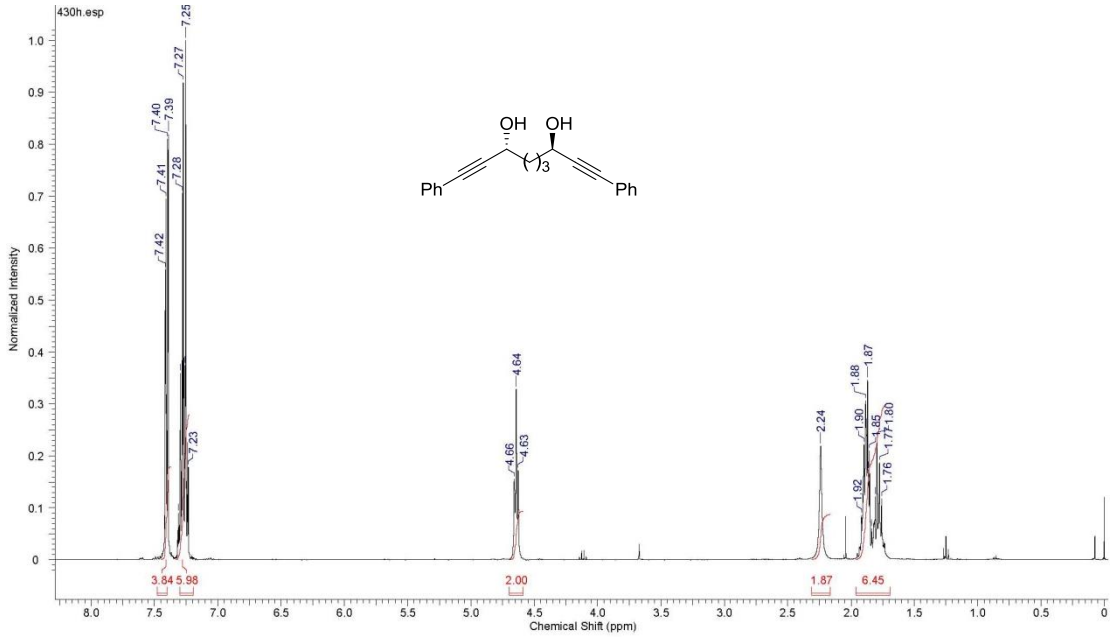
^{1}H NMR of *R,R*-**202**.



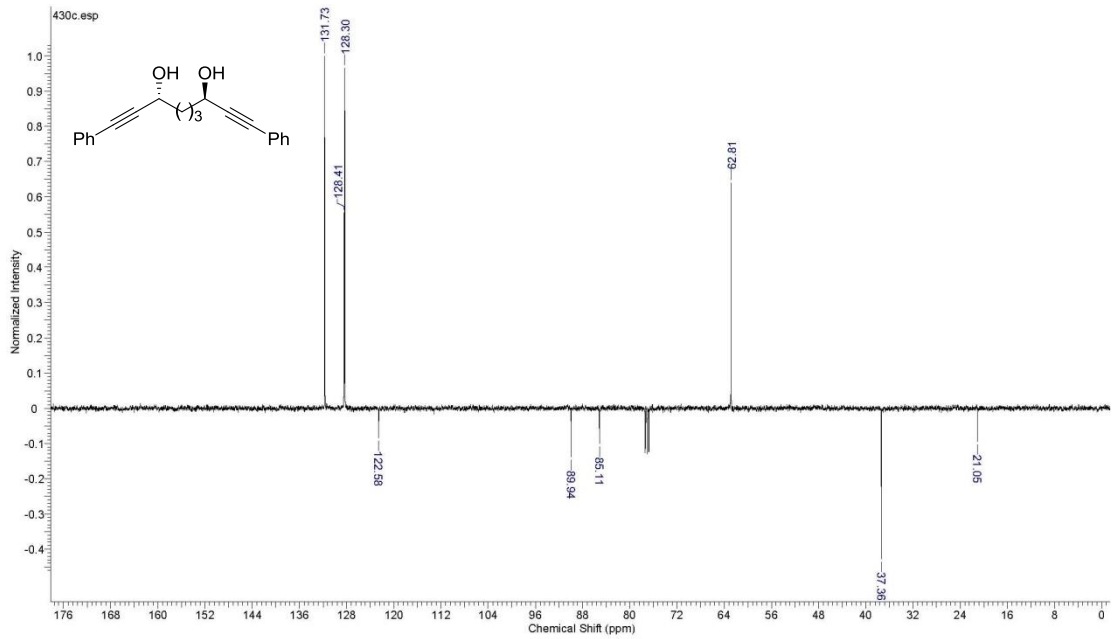
^{13}C NMR of *R,R*-**202**.



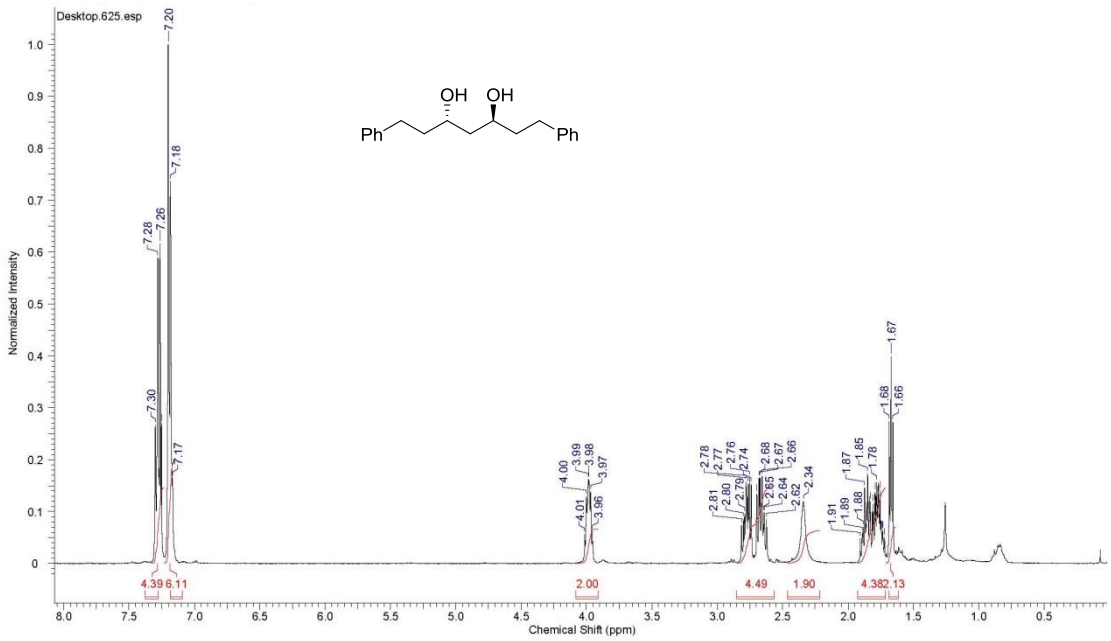
^{1}H NMR of *R,R*-**205**.



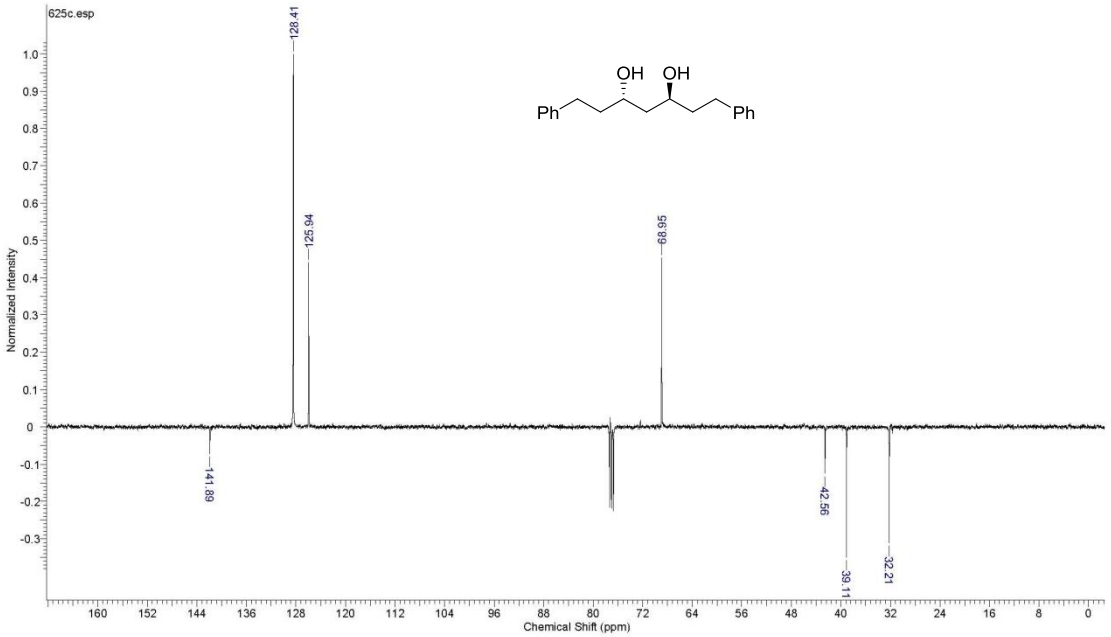
^{13}C NMR of *R,R*-**205**.



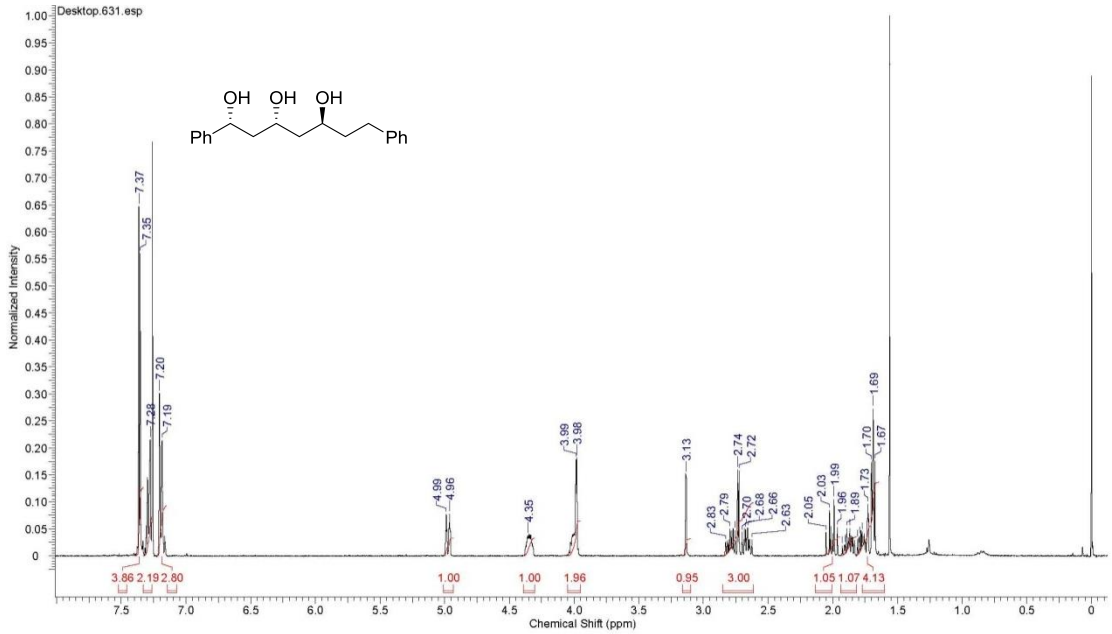
^{1}H NMR of (-)-yashabushidiol B **219**.



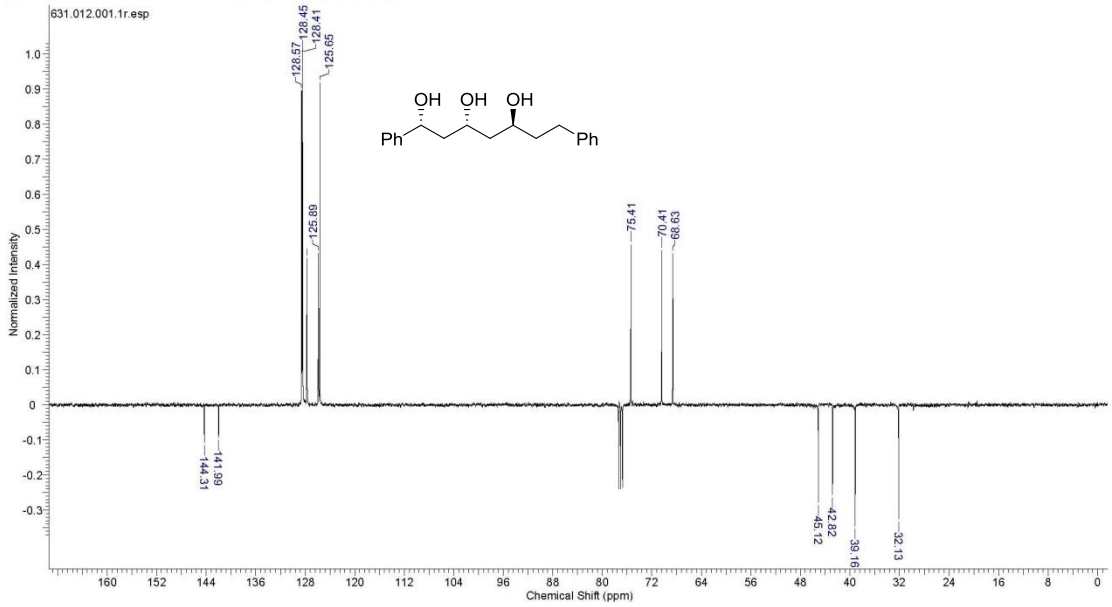
^{13}C NMR of (-)-yashabushidiol B **219**.



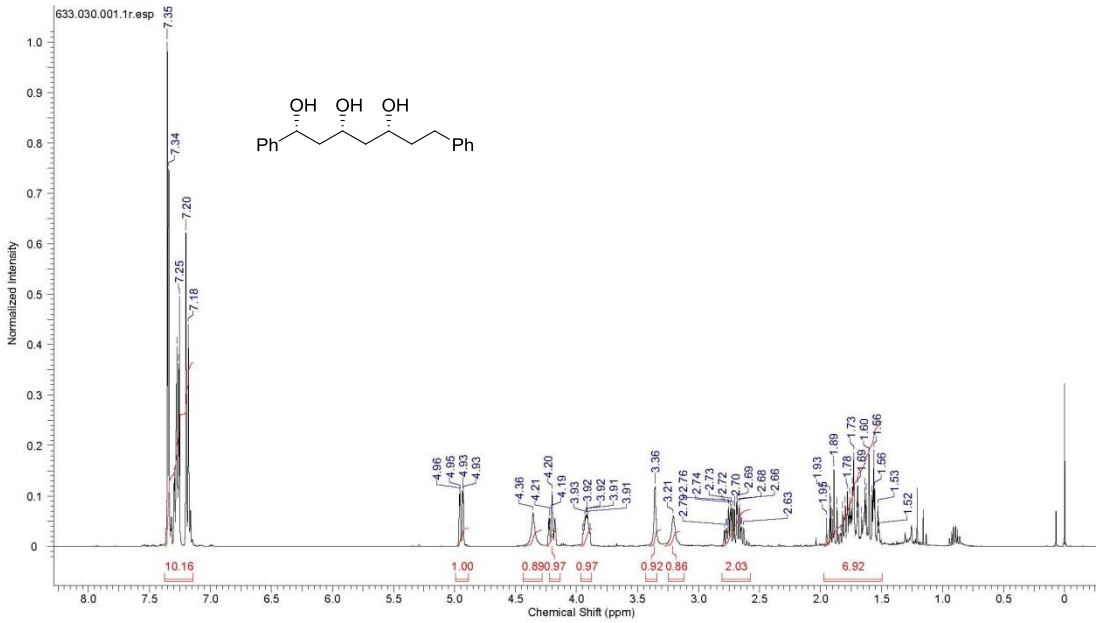
^{1}H NMR of yashabushitriol **129**.



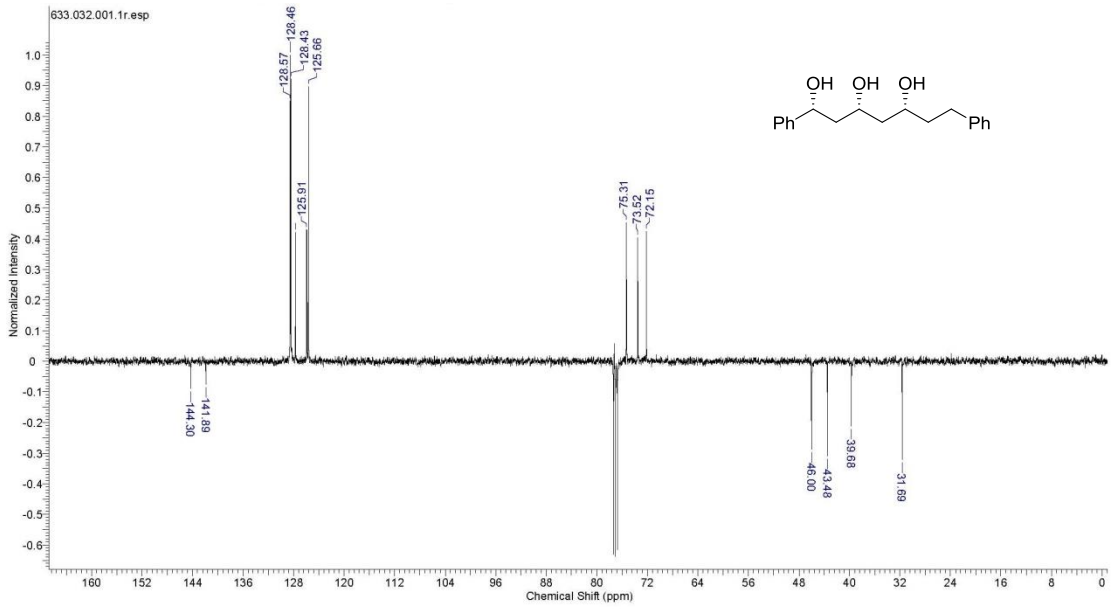
^{13}C NMR of yashabushitriol **129**.



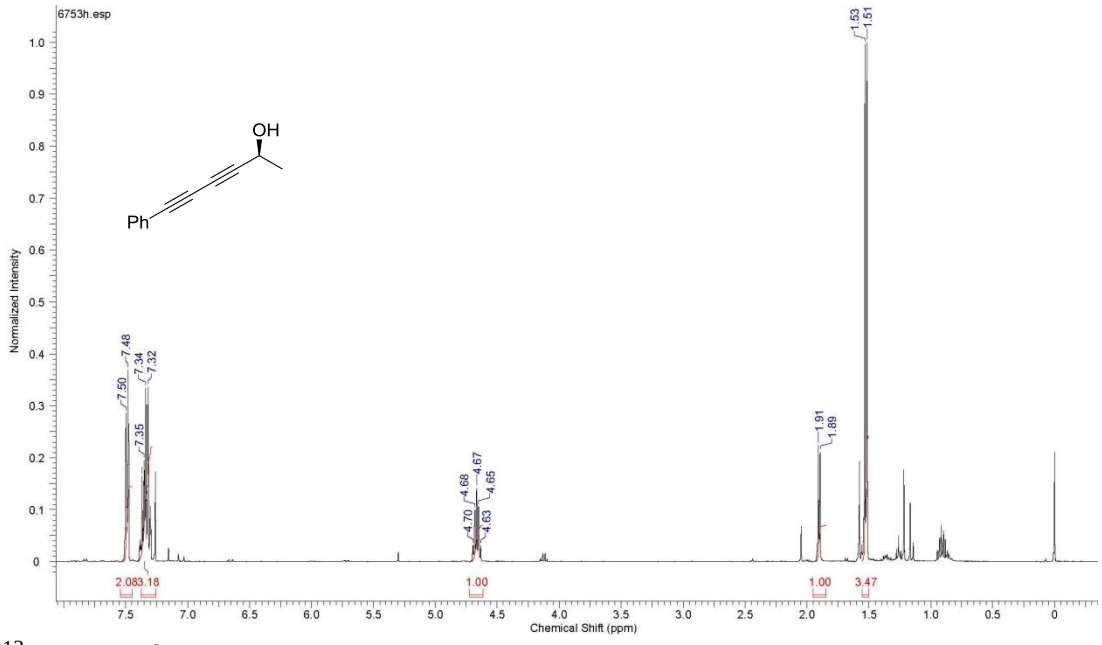
^{1}H NMR of 5-*epi*-yashabushitriol 5-*epi*-**129**.



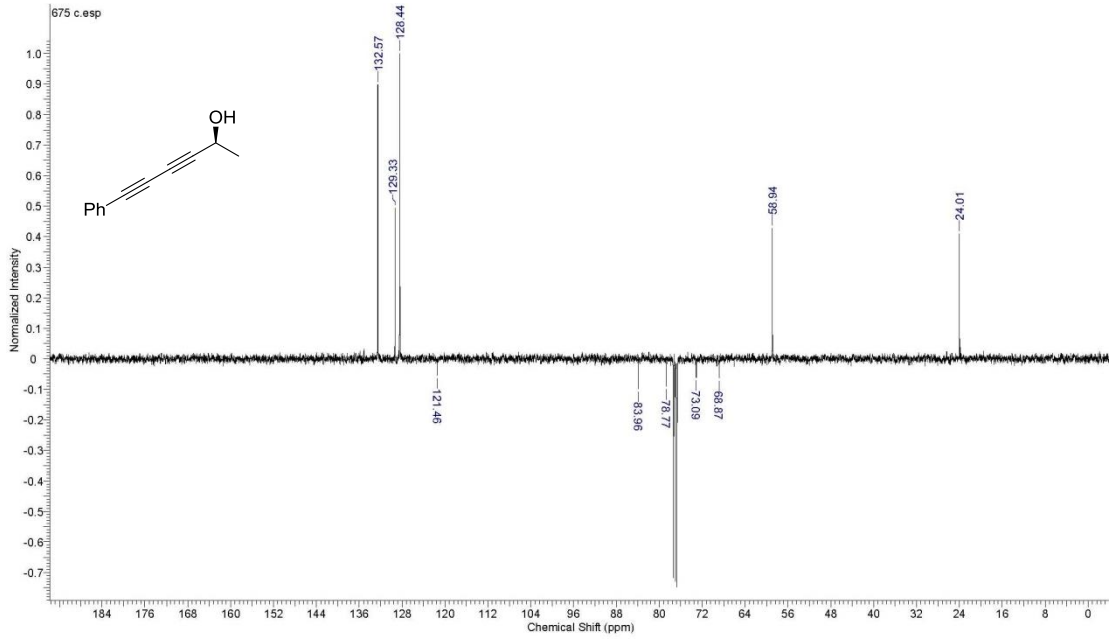
^{13}C NMR of 5-*epi*-Yashabushitriol 5-*epi*-**129**.



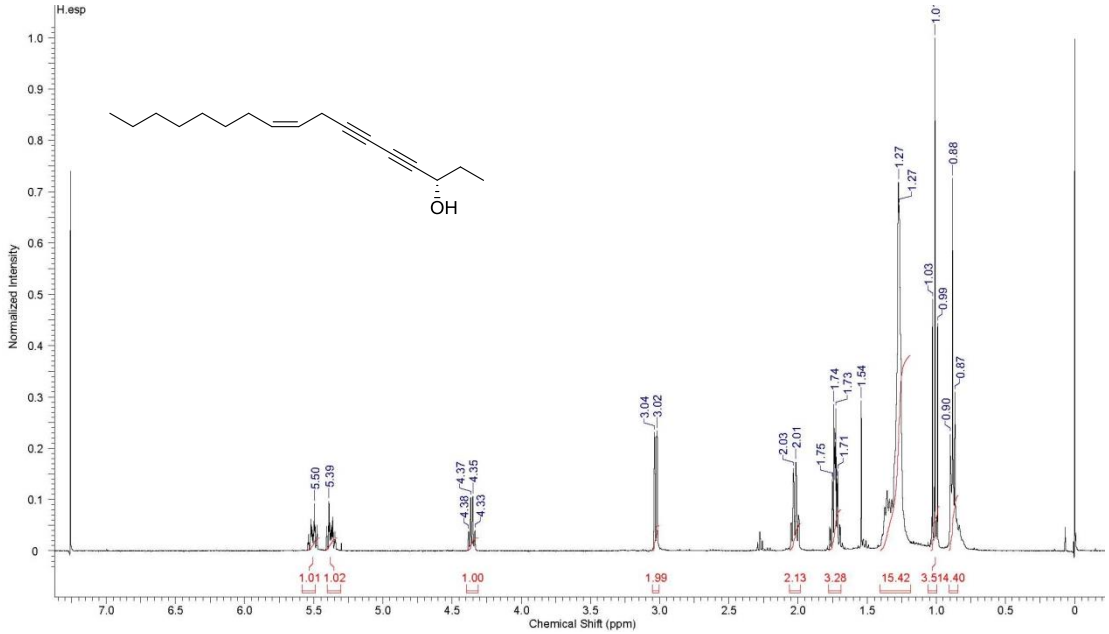
^{1}H NMR of *S*-**215**.



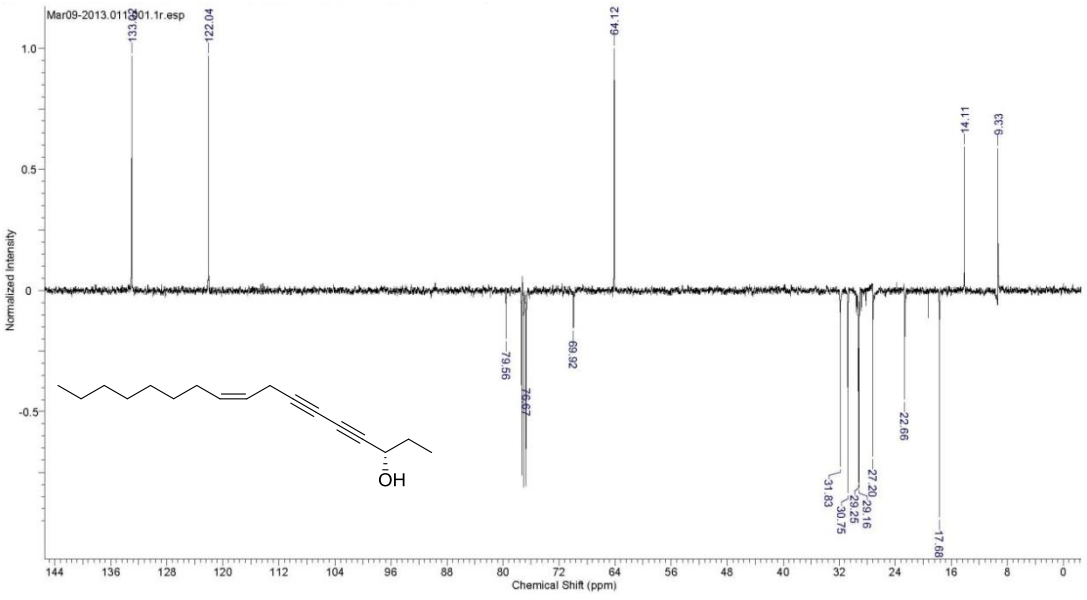
^{13}C NMR of *S*-**215**.



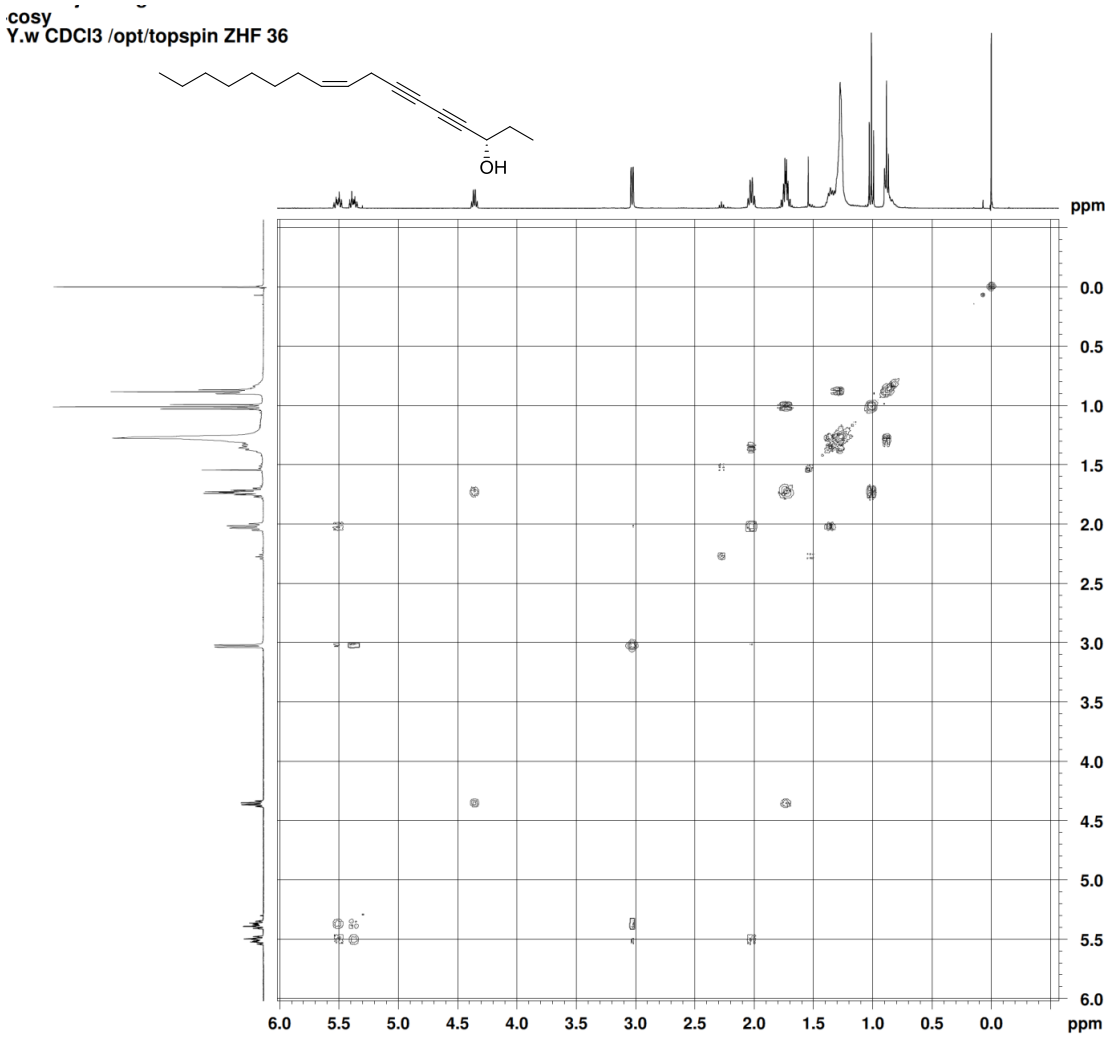
^{1}H NMR of panaxjapyne A **239**.



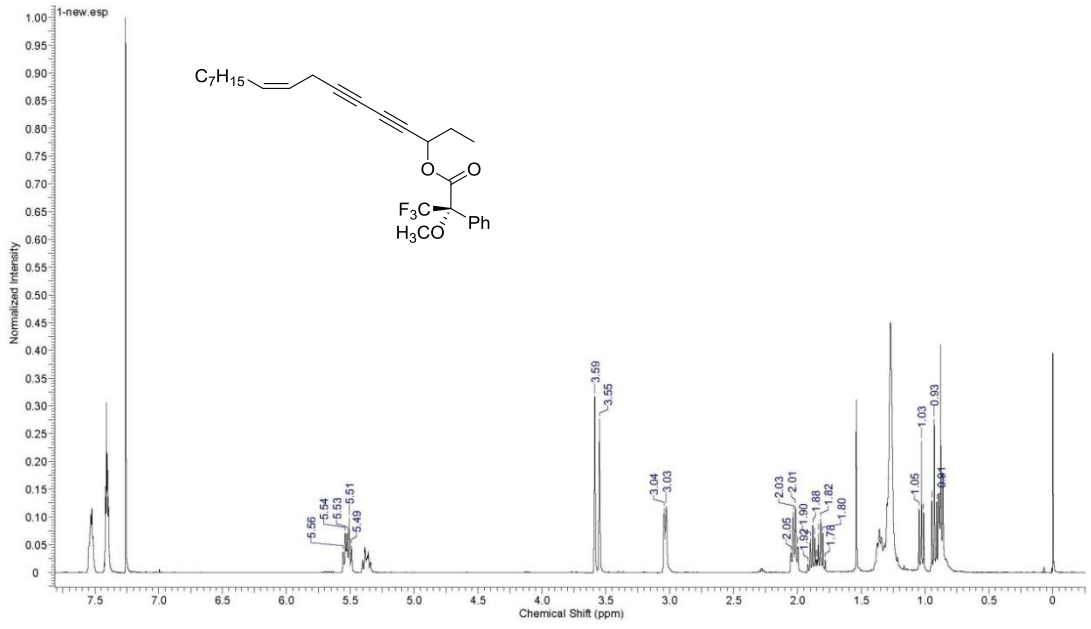
^{13}C NMR of panaxjapyne A **239**.



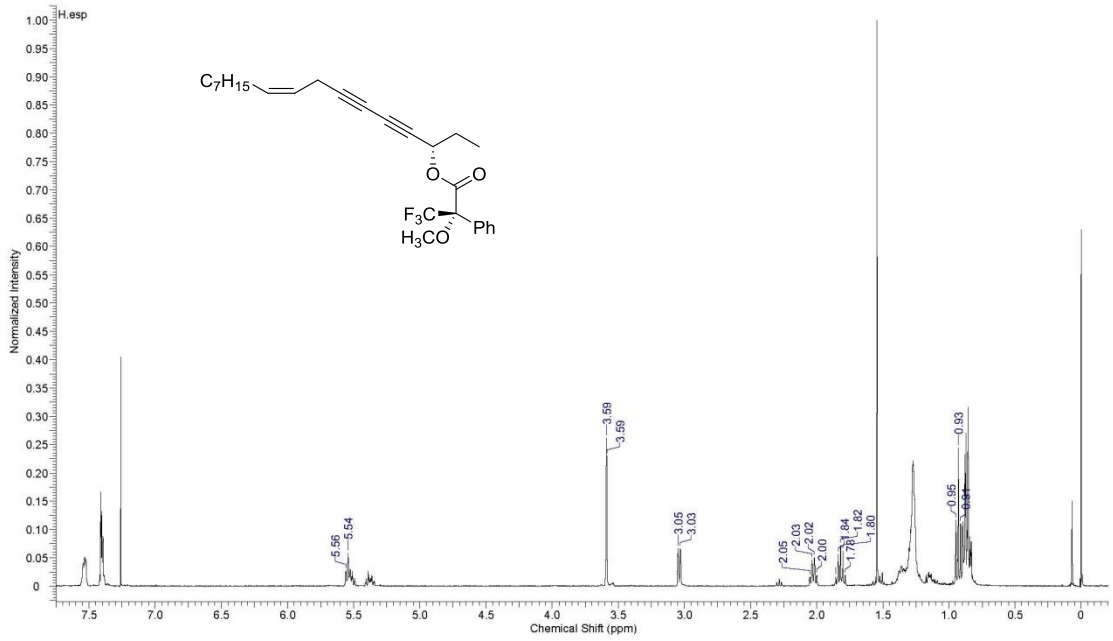
^{1}H-^{1}H Cosy of panaxjapyne A **239**.



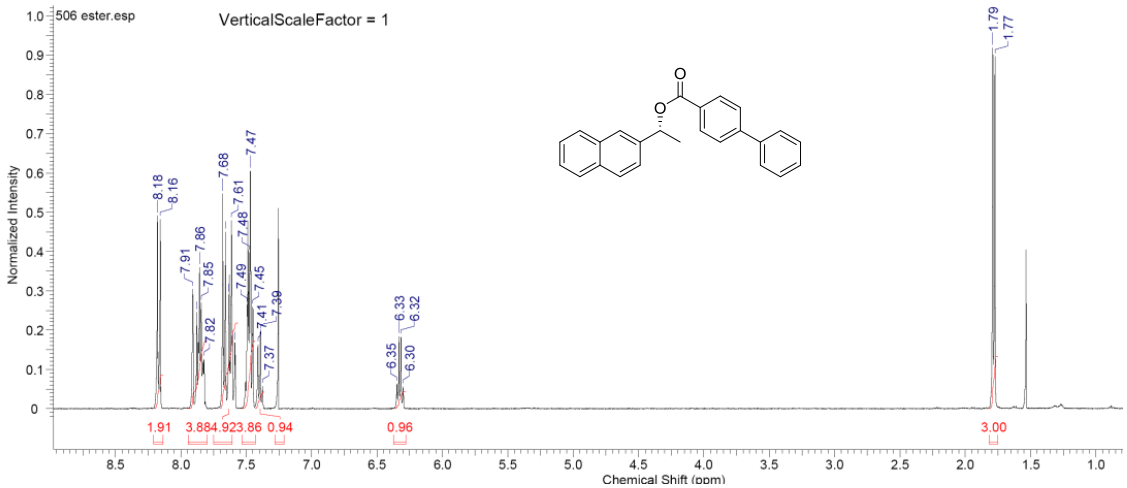
^{1}H NMR of Racrmic panaxjapyne A-(*S*)-MTPA ester



^{1}H NMR of panaxjapyne A-(*S*)-MTPA ester



^{1}H NMR of *R*-**243**.



^{13}C NMR of *R*-**243**.